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Evaluation and Management of the Heavily Irradiated Individual[1,2]

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INTRODUCTION

Considerable experience with the acute radiation syndrome in man, in varying degrees of severity, has been gained as a result of the exposure of the Japanese at Hiroshima and Nagasaki (1); of the Marshallese at the Pacific Proving Ground (2); of patients given total body irradiation for therapy of malignant conditions (3); of patients treated in this fashion to depress antibody production preparatory to homografting of tissue (4, 5); of patients given internal emitters in the course of therapy (6, 7); of workers accidentally exposed in accidents involving fissionable material (7-14) and of workers involved in non-nuclear radiation accidents such as the recent Lockport Klystron-tube incident (15). This degree of experience in human beings, coupled with the vast amount of animal experimentation that has been done, removes any justification for surrounding the syndrome with an aura of mystery. The pathogenesis is better understood than is that of many of the clinical conditions dealt with routinely and effectively in the course of medical practice. The therapeutic principles involved are thus based on known pathologic changes, and as with other disorders, the type of therapy and its time of administration depend on a complete and continuing clinical appraisal of findings in the individual patient. The heavily irradiated individual, managed by physician well versed in the handling of patients with blood dyscrasias, would receive excellent therapy for his disorder even in the complete absence of knowledge that radiation was the causative factor.

The aim of the present paper is to develop guidelines for management of the heavily-exposed individual based on the pathogenesis of the acute radiation syndrome, and on the use of measures demonstrated to be beneficial.

1. Supported by the U. S. Atomic Energy Commission.

2. From the Medical Research Center, Brookhaven National Laboratory.

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PATHOGENESIS OF THE ACUTE RADIATION SYNDROME

The disorder consists actually of a complex of overlapping syndromes, the presence and severity of which is dependent on the physical dose received (16-20). The primary interaction between radiation and cellular constituents is not well understood. However the cardinal early results of damage to the individual cell are well known. These are direct cell deaths seen in some cell types within hours of exposure, and a reduction in proliferative capacity. Cells may be unable to divide, or division may result in abnormal daughter cells that die or are unable to reproduce beyond one or two generations. These effects on cells result of course in organ changes. In general tissues with greater cellular turnover rates are more radiosensitive. The relative importance to the clinical picture of injury to an organ is related primarily to the "radiosensitivity" of the tissue, but not entirely. Hypoplasia of the radiosensitive gonads is compatible with life. Marked depletion of the lymphocytic system can be tolerated for relatively long periods. However aplasia of the bone marrow or gastrointestinal mucosa produces metabolic disturbances which are prompt hazards to life. These disturbances can be managed for short periods; ultimate survival depends upon regeneration. Unquestionably all organ systems are affected by heavy exposure. The relative sensitivity of organ systems determines the clinical syndrome observed. After very high doses, injury to the central nervous system produces a typical syndrome that results in death usually within a short time (hours). If death does not occur or if the dose is lower, injury of the gastro-intestinal mucosa with resulting atrophy results in loss of plasma into the bowel, homoconcentration, vascular collapse and death within days in untreated cases. With successful treatment or after still lower doses that only produce a temporary GI syndrome, marrow hypoplasia will be produced. The marrow depression results in a pancytopenia that is both time and dose dependent. The depletion of neutrophils[1] is correlated with increased susceptibility to infection, and the thrombopenia with bleeding tendency. In the absence of therapy, deaths from these cardinal manifestations may result usually between the 2nd and the 6th week.

CLASSIFICATION OF PATIENTS WITH THE ACUTE RADIATION SYNDROME

Basis for Patient classification.

A rough classification of patients who have received heavy exposure into groups, according to dose received or according to the symptom complex presented and its time of onset is given in Table 1. This must be arbitrary, since with increasing dose, and within limits among individuals receiving the same physical dose, the signs and symptoms presented and their degree of severity present a continuum. Hence the present classification is presented for purposes of orientation in respect to broad aspects of diagnosis, prognosis and therapy. Physical dose, as will be shown, is a poor basis for classification. Classifications on the basis of the clinical picture have been presented (16-20). It is quite clear that

1. All known defenses against infection are adversely affected. Defects in hemostasis are correlated with the thrombopenia. Clinical infection and purpura are related to the depletion of neutrophils and platelets, respectively.

therapy should not be based on physical dose or the category into which a patient has been placed. Therapy is guided only by the daily appraisal of clinical and laboratory findings, and should be given only when clearly indicated, and not prophylactically.

Dosimetric considerations.

Dose estimates aid to some degree in considerations of early patient management and of possible late effects, and the more dosimetric information collected the greater will be the degree of aid in future accidents. Thus every reasonable effort should be made to obtain as accurate dose estimates as is possible, as early as possible. Health physics personnel have been most cooperative and ingenious in obtaining dose estimates in previous accidents (8-12, 14). Such estimates are of limited value in patient management, however, for the following reasons: first, it is almost axiomatic that suitable dose measuring devices are absent when an accident occurs, and the retrospective dose evaluation usually is not completed until after the time for optimal usefulness. Early dose estimates may be in error by a considerable factor. Second, two or more kinds of radiation usually are involved, the relative effectiveness and degree of additivity of which are not known. Third, considerable disagreement on dose-effect relationships in man exists at present. Fourth, if the statistical dose-effect relationships were known for man, it is still impossible to determine in advance the sensitivity of a single individual. Fifth, geometry and shielding effects leading to gross inhomogeneities in absorbed dose may be difficult or impossible to evaluate. For these reasons, a dose estimate should be given the same relative importance as any single clinical or laboratory finding in medicine—to be considered critically in the overall evaluation, but to be discarded if it is not consistent with the general clinical picture. For the above reasons and to indicate its questionable value dose in Table I is given as "r" in ranges, rather than in the more precise "rads".

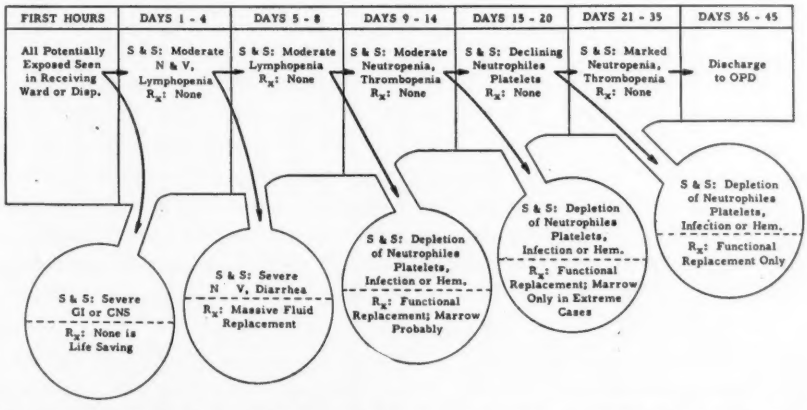
FIRST HOURS
DAYS 1 - 4
DAYS 5 - 8
DAYS 9 - 14
DAYS 15 - 20
DAYS 21 - 35
DAYS 36 - 45
All Potentially Exposed Seen in Receiving Ward or Disp.
S & S: Moderate N & V, Lymphopenia Rx: None
S & S: Moderate Lymphopenia Rx: None
S & S: Moderate Neutropenia, Thrombopenia Rx: None
S & S: Declining Neutrophiles Platelets Rx: None
S & S: Marked Neutropenia, Thrombopenia Rx: None
Discharge to OPD
S & S: Severe GI or CNS
Rx: None is Life Saving
S & S: Severe N V, Diarrhea
Rx: Massive Fluid Replacement
S & S: Depletion of Neutrophiles Platelets, Infection or Hem.
Rx: Functional Replacement; Marrow Probably
S & S: Depletion of Neutrophiles Platelets, Infection or Hem.
Rx: Functional Replacement; Marrow Only in Extreme Cases
S & S: Depletion of Neutrophiles Platelets, Infection or Hem.
Rx: Functional Replacement Only

Fig. 1. Schematic outline indicating the times at which cardinal manifestations become evident in the heavily-exposed individual, and management indicated at these times.

TABLE 1. CLASSIFICATION OF PATIENTS WITH THE ACUTE RADIATION SYNDROME

Dose range	*Early, or prodromal signs and symptoms*	*Definitive signs and symptoms*	*Prognosis*
Less than 200 r	No signs or symptoms, or mild nausea and vomiting, lasting 24 hours or less. Lymphocytes above 1500/mm.	No systemic manifestations, depression of neutrophils and platelets, fourth and fifth week.	Essentially 100 per cent survival in the healthy adult.
200, to 400 r or 500 r	Nausea and vomiting in nearly all exposed; intermittent and lasting 2 to 4 days or more. Lymphocytes above 1000/mm^3.	Severe neutrophil and platelet depression 3 to 5 weeks; evidence of infection and hemorrhage may appear.	No, to 100 per cent mortality in untreated; rare fatality with adequate functional replacement therapy if needed.
400 or 500, to 900 r	Severe nausea and vomiting; intractable. Lymphocytes less than 500/mm^3.	Severe neutrophil and platelet depression days 10 to 20, or earlier. Severe systemic manifestations, evidence of hemorrhage and infection within 1 to 3 weeks.	High per cent mortality even in those given functional replacement therapy; effectiveness of bonemarrow therapy not yet evaluated.
Greater than 900 r	Severe and intractable nausea and vomiting; CNS symptoms at higher dose levels, lymphocytes virtually zero.	Continuous with prodromal signs and symptoms; evidence of severe gastrointestinal damage, CNS damage at higher doses.	100 per cent mortality probable, independent of therapy given. Marrow therapy trial indicated.

MANAGEMENT OF THE INDIVIDUAL PATIENT

General considerations.

With the acute radiation syndrome, non-medical personnel generally expect a precise prognosis and therapeutic outline soon after exposure, in contrast to the usual systematic and continuing analysis of a disease course that is expected of the physician. Radiation exposure should not be considered an extreme emergency. There is no justification for hasty therapeutic procedures done without careful consideration. It will be apparent within hours or days whether the exposure was so low that no therapy will be required, or so high that no therapy will help. For patients in intermediate exposure ranges, days and even weeks will pass before a need for therapy may exist, and before the prognosis can be evaluated. Thus in many patients statements on prognosis must be extremely guarded for weeks. The most challenging therapeutic problem is related to depression of the bone marrow and its sequelae produced by pancytopenia. The *need* for therapy, and the *time* at which it should be considered, are related to depletion of peripheral blood elements, and to the time at which the depletion occurs.

A general guide for the type of therapy indicated, and the time after exposure when it may be needed are given in Fig. 1 There is a "peeling off" in time, as signs and symptoms appear which define the applicable therapy. "Functional replacement therapy" is employed here to indicate the use of antibiotics to augment impaired defence mechanisms, and of fresh platelets to control bleeding. "Tissue replacement" or "bone marrow" therapy indicates the use of bone marrow or fetal tissue for transplantation.

For illustrative purposes in discussing management, serial blood counts[1] from three groups of human beings heavily exposed at different dose levels are shown in Figs. 2, 3 and 4. These include the Marshallese exposed to fallout radiation in March, 1954, (2), and individuals exposed in accidents at Oak Ridge in June, 1958 (11) and Yugoslavia in October 1958 (12). The Marshallese showed moderately severe neutropenia and thrombopenia in the 5th week, but developed no signs or symptoms that could be attributed to this depression. None died. Although individuals exposed at the Oak Ridge accident showed severe blood depression on approximately day 30, and some developed signs of infection and hemorrhage, none died even though no treatment was felt to be indicated nor given because of the exposure. The signs and symptoms in the Yugoslav patients were more severe than those in the Oak Ridge patients and one died. Functional replacement therapy and bone marrow infusions were given to all of these patients.

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1. It is obvious that different methods of blood counting are employed in different laboratories, and therefore the values obtained, and the limits of error will vary greatly. This reservation must be kept in mind when comparing counts. The relative changes within a laboratory of course will be more reliable than will be a comparison of counts from laboratory to laboratory.

Days 1 to 4. When first seen, a complete physical examination, urinalysis and blood counts should be done on any patient suspected of having been exposed, both as an initial baseline and for medical-legal purposes. In general (but not always) it will be known within hours, from the circumstances of the accident, if radiation was involved, and the possible order of magnitude of dose. In the Lockport Klystron accident, reports from the accident scene for many hours indicated insignificant exposure, when in reality very heavy exposure had been sustained. Health Physics personnel, if not already present should be called. If nuclear fission and thus neutron radiation was involved, blood samples for determination of induced radioactivity should be taken propmptly for dosimetric purposes. Total-body counting, if feasible, should be done in close association with health physicists.

If the patient shows no evidence of nausea or vomiting, or only mild nausea over the first hours to days, the chance of exposure requiring later therapy is minimal, but not absent. A failure of the lymphocyte count to fall by more than a few per cent, or to less than 1.500/mm^3, would tend to confirm this opinion. The patient with any appreciable fall in lymphocyte count should be watched carefully on an outpatient basis over the next 6 weeks, and periodically thereafter as indicated. The neutrophil and platelet count may fall considerably during the 4th to 6th week, and observations should be made frequently (daily if change is rapid) at these times.

If the patient is nauseated or vomits, or if his lymphocyte count drops by more than 50 per cent, or to approximately 1200/mm^3 or less, he should be hospitalized at once for observation. If the nausea and vomiting is not severe and is transient, only appropriate symptomatic therapy is indicated. If the nausea and vomiting appear within hours and continue, or are accompanied by fever and diarrhea, steps to correct fluid imbalance should be considered. A lymphopenia below 500/mm^3 in the first 2 or 3 days, in the absence of other signs and symptoms is grounds for hospitalization and observation. If evidence of CNS involvement is present (ataxia, disorientation, stupor, convulsions), the prognosis is grave indeed. Therapy is symptomatic, and discussion of functional or tissue replacement therapy if total body radiation has been sustained[1] are academic since no effective therapy is known. Death can be expected within hours to days.

It should be noted that the initial lymphocyte counts of individuals exposed at Oak Ridge all remained above approximately 600/mm^3, while the counts of the Yugoslav's were below 500/mm^3 by the 3rd day. The individual (V) whose initial lymphocyte count approached zero, died despite vigorous therapy.

Days 5 to 8. It will become apparent from the symptomatology and blood counts that some hospitalized patients can be released to the outpatient department for careful followup. However, those with moderate and transient prodromal symptoms, and lymphopenia, should be retained in the hospital. Patients essentially asymptomatic at this time, and without severe disturbance of the neu-

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1. Large doses may be delivered to the head, compared to the body (as in the Lockport Klystron accident). Thus prognostications must be guarded under even these apparently extreme conditions, unless it is clear that essentially uniform total body irradiation was involved.

trophil or platelet count, may develop severe signs and symptoms later. The presence of additional signs and symptoms at this time (lassitude, vague abdominal pains or gastro-intestinal upset) increase the probability of heavier exposure.

If nausea and vomiting have continued unabated, with diarrhea, fever and abdominal pain, fluid, electrolyte, functional and tissue replacement therapy may all be indicated. From animal studies (21), the amount of fluid and electrolytes

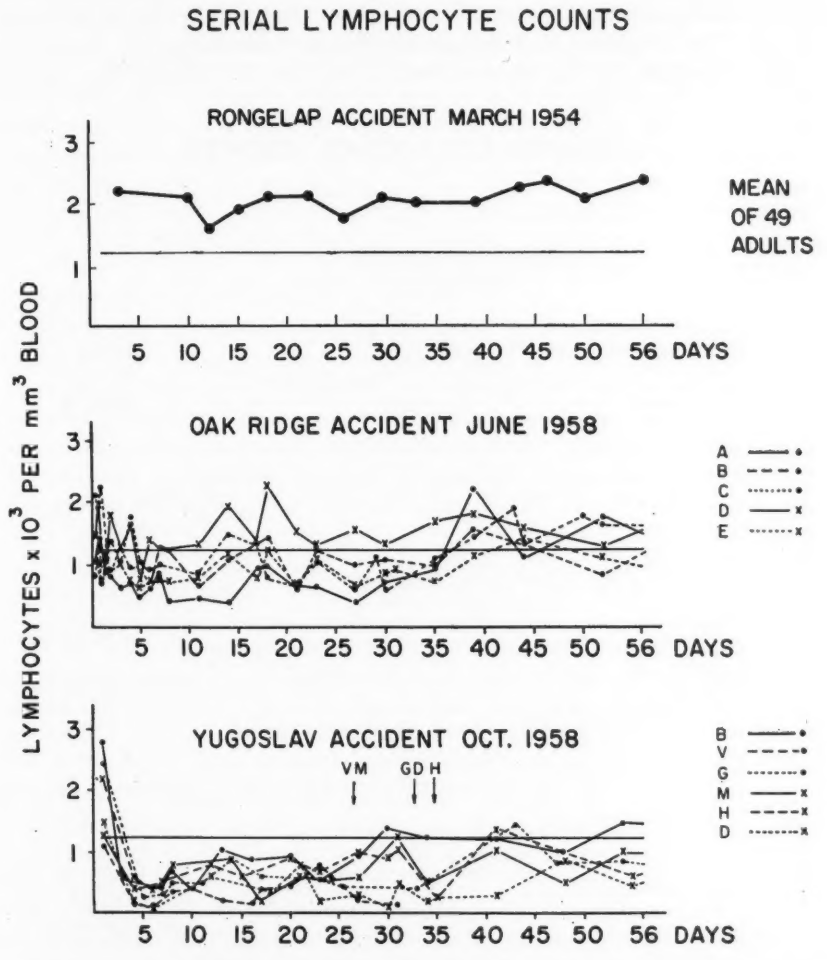

Fig. 2. Comparative serial lymphocyte counts in the heavily exposed Marshallese (from Ref. 2), Oak Ridge (from Ref. 9) and Yugoslav (from Ref. 10) individuals. The Marshallese and Oak Ridge patients received no therapy for the radiation exposure; none died. The apparently more heavily exposed Yugoslav patients received functional and marrow replacement therapy; one died. The arrows above the graphs for the Yugoslav patients indicate the times at which bone marrow transfusions were given.

required is enormous; however the bowel appears to be capable of regeneration after very high dose levels. If the bowel has been damaged sufficiently to warrant this type of therapy, severe marrow aplasia and pancytopenia will develop also. Functional replacement and marrow therapy may be considered. Although combined therapy for bowel and marrow effects have been efficacious in the rodent, it is extremely doubtful that a patient this heavily exposed would survive with even the most extensive therapy.

Day 9 to 14. By this time patients manifesting severe bowel damage by virtue of sufficiently high exposure will either be receiving therapy or will have expired. The diagnostic and therapeutic problems remaining are concerned mainly with aplasia of the marrow, and its sequelae. Peripheral blood counts

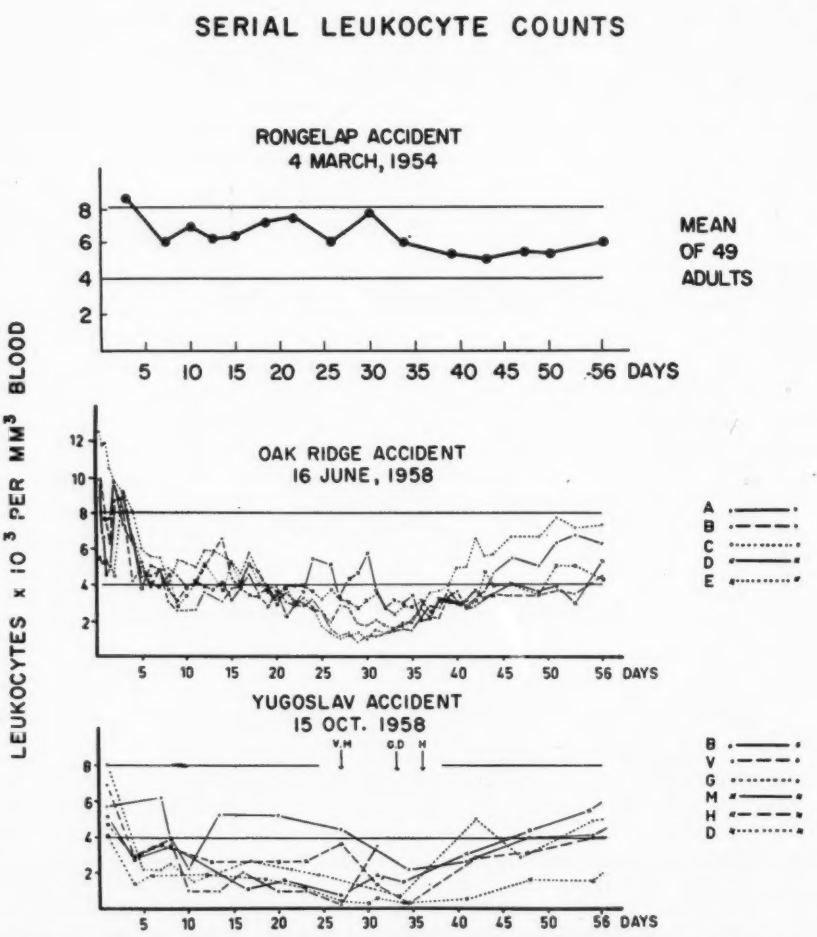

Fig. 3. Comparative serial total leukocyte counts in the Marshallese, Oak Ridge and Yugoslav individuals.

(neutrophils, platelets, hematocrit) should be followed daily, and plotted. In the absence of significant neutropenia or thrombopenia, no therapy will be needed and in fact would be contraindicated unless warranted by other clinical findings. If the neutrophil and platelet counts approach zero, and/or any evidence of infection or of hemorrhage (petechiae, microscopic hematuria) is present, functional replacement therapy should be started at once. If neutrophils or platelets have been at the zero level for 24 hours, such therapy should be started in the absence of specific evidence of infection and/or hemorrhage. The urine sediment should be examined at least daily for microscopic hematuria. With neutrophil or platelet depletion this early following exposure, infection even with normally non-pathogenic organisms, and hemorrhage are virtual certainties. Strict isolation precautions should be started as soon as it is suspected that the individual may require functional or tissue replacement therapy. When, from the plot of neutrophil counts, it is evident that the value may approach zero, strict isolation precautions are of great importance. Gown and masks should be required, and the number of persons allowed to enter the room should be severely limited. The individual's defenses against infection are almost completely absent, and he may be considered a very favorable "culture medium" for organisms. Thus every effort to protect should be taken.

Further remarks should be made with regard to the nature, and efficacy of functional replacement therapy before specific tissue or bone marrow therapy is considered. The use of antibiotics is obviously well established in clinical medicine. Antibiotics alone have been shown to be markedly effective in heavily irradiated mice (22), less so in rats (23) and dogs (24). The value of fresh platelet transfusions in clinical thrombopenias is well known, and their ability to stop radiation-induced bleeding has been demonstrated in dogs (25-28) and in rats (29). Their value in dogs is indicated in Fig. 5 (from ref. 27). Following doses of the order of 550 r, hemorrhage appears around the 9th day and can be demonstrated and quantified by cannulating the thoracic duct (27, 28). The normally white lymph is grossly bloody. It is apparent from the figure that fresh platelets were capable of circulating, and of "turning off" hermorrhage once it had begun. It is equally apparent that lyophilized platelets had no such effect. Disintegrated fresh platelets did not effect hemostasis, even though the clotting defect was corrected to a degree as indicated by *in vivo* tests (30). The efficacy of, and necessity for fresh blood or platelets to effect hemostasis is thus obvious, and it is most probable that these results apply to man.

In irradiated animals the probability of infection and death has been correlated with neutropenia (31, 32). In this paper a similar correlation has been implied and there is no reason to doubt it. Since infections may occur in non-irradiated individuals without neutropenia (usually due to pathogens, not commensal organisms) it is not possible to prove in every instance whether the infection would have occurred in the absence of the exposure to radiation. However the probability will increase with the neutropenia and in any event all infections must be treated upon appearance.

Additional important information relating to functional replacement therapy can be derived from studies on an effective therapeutic regimen for the

acute radiation syndrome produced in dogs (33). As indicated, the use of antibiotics and fresh platelets in marrow hypoplasia is well based in clinical experience. However, the degree to which they are effective following massive exposure (by what factor their use will raise the dose level at which survival is possible) cannot be determined on man, and thus animal studies involving the use of antibiotics and fresh platelets were undertaken (33). By use of functional replacement therapy only, a near "LD_{100}" dose can be converted into an "LD_0" dose, or the dose at which survival is possible can be approximately doubled. The regimen used is indicated in Fig. 6 (taken from Ref. 33; 400 r is an $LD_{95\text{-}100}$

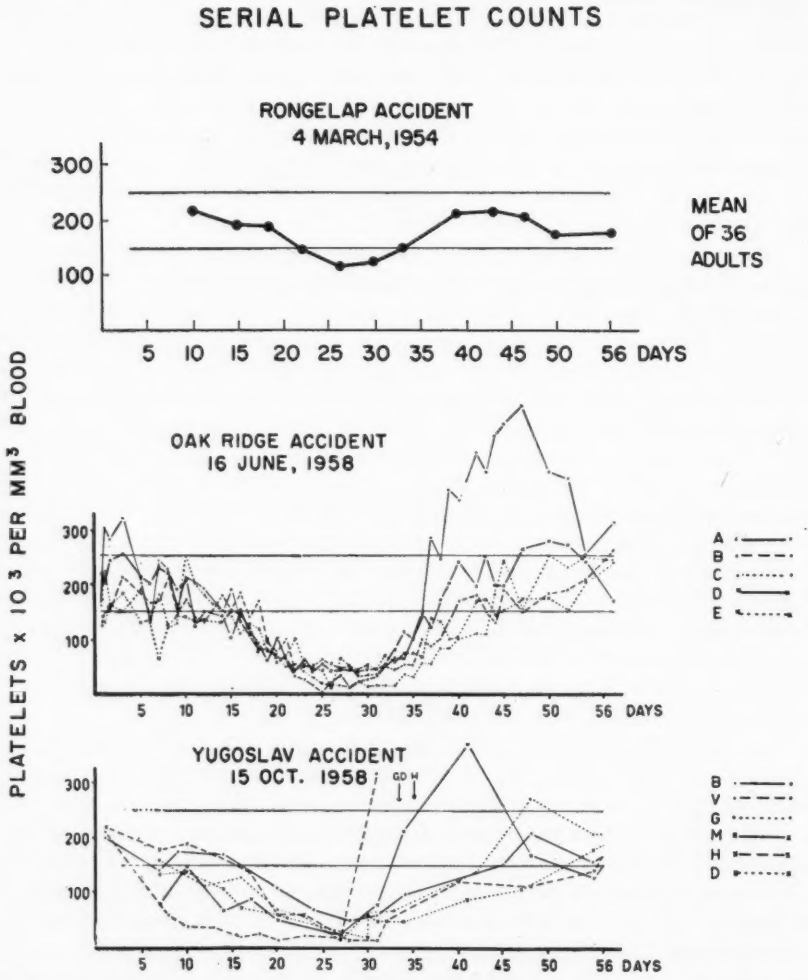

Fig. 4. Comparative serial platelet counts in the Marshallese, Oak Ridge and Yugoslav individuals.

dose). Although the time sequence of events is shortened in the dog compared to man, several points are emphasized by these studies that should be kept in mind when treating the human being. The animals were well, and no therapy was given or indicated until both the neutrophil and platelet counts had reached essentially zero. At this time the temperature rose, and usually oxytetracycline was started in approximately twice the dose, on a weight basis, usually employed in man. The one antibiotic controlled the infection only for 4-5 days, at which time developing resistance or an "escape" occurred, and it was necessary to change antibiotics with still another change when this antibiotic was not longer effective. When the neutrophil count began to rise, antibiotics were no longer necessary. This "escape", well known in clinical medicine, would argue strongly for withholding antibiotics until actually needed since there is a limited number of effective antibiotics, and such therapy may be required over a period of two or more weeks. If organisms are cultured, this may aid in choice of antibiotics. In the absence of positive cultures or other considerations, the antibiotic regimen indicated in Fig. 6 may be considered for human beings.

Platelet transfusions were given as indicated in Fig. 4. Fresh whole blood (out of the body less than an hour) was given if the hematocrit was below normal; platelet-rich plasma was given if the hematocrit was normal. Since transfusion to control bleeding prevented severe anemia, transfusions to correct this condition were not needed. Platelets were transfused in amounts corresponding to the number present in 20-40% of the blood volume of the dog. These quantities, if all circulated, would raise the platelet count from the near zero level to between 60,000 and 120,000/mm^3. Since this raised the count to the order of 40,000/mm^3, approximately 1/3-2/3 of the platelets transfused appeared viable. Following transfusion, the platelet levels dropped by a fraction of about 0.5/day, requiring another transfusion in approximately 4-5 days. These platelet levels maintained by transfusion were adequate to prevent significant hemorrhage. During this course of therapy the dogs were active and "clinically" quite well, as contrasted to the extremely ill non-treated dogs for the several days prior to death on approximately days 10 to 15. No difficulties with anti-platelet antibodies was encountered; however in initial studies (7) a potent anti-platelet substance developed in dogs transfused daily with fresh platelets commencing 5 days after exposure to 600 r. After about 7 days platelets failed to circulate and an agglutinin was present for all canine platelets tested. A similar observation of failure of platelets to be effective after prolonged transfusion therapy was noted in a woman who had radiation-induced thrombopenia (7). In this patient studies on anti-platelet substances were equivocal with titres less than 1/8 in contrast to greater than 1/124 in the dogs.

Whereas corticosteroids are beneficial in some types of purpura they are contraindicated in radiation thrombopenia because of increased risk to infection, suppression of adrenals, and in empiric studies in animals have increased the mortality rate.

The decision to attempt bone marrow transplantation will be particularly difficult at this time. With the absence of neutrophils or platelets from the blood this soon following exposure, it is probable that some may not survive even with

adequate functional replacement therapy. The presence of severe symptoms and signs not immediately relatable to marrow depression (headache, abdominal pain[1], oliguria or anuria, extreme lassitude, diaphoresis, insomnia) might incline one in the direction of giving bone marrow, and if given, adequate amounts of homologous marrow (4), preferably by direct transfer from donor to patient (12) should be employed. Examination of serially aspirated marrow will aid in this decision. The presence of a completely aplastic marrow would argue for transfusion; evidence of cellularity or of beginning regeneration in a previously aplastic marrow would argue against it. In the decision, the questionable status of the efficacy of marrow homografts in man, the probability of survival with functional replacement only, and the possibility of adverse late immune reactions must be taken into account. Some of these factors are considered below:

The striking efficacy of marrow transplantation in the rodent has been demonstrated repeatedly. The transfusion is effective at dose levels above the "LD_{100}"; less effective or even harmful at lower dose levels, presumably because of incomplete destruction of the host's immune mechanism and resultant host-donor reaction. With some homologous transfusions and with heterologous transfusions, although there may be an early protective effect, many animals later develop the "secondary disease" or "wasting disease". This disease, presumably related to immunological reactions between the two foreign tissues, results in delayed deaths in the animals. Although autologous marrow transfusions have been of value in the dog, homologous transfusions have been not at all or rarely (34) successful. In the United States, there appears at present to be no unequivocal case of a successful marrow homograft in patients given large doses of total body radiation, and bone marrow, for therapeutic reasons. The Yugoslav radiation casualties were treated in Paris with homologous marrow, and evidence has been presented that the marrow "took" and was instrumental in the survival of the patients (12). Some have regarded the evidence for a "take" as inconclusive, and feel that survival would have occurred even if marrow transfusions had not been given. From Fig. 2, it will be noted that the data of the marrow transfusions (indicated by arrows above the graphs) coincided with the time when the peripheral blood counts were either increasing, or would increase spontaneously in a short time.

The same authors have presented extensive evidence for successful homologous marrow transfusions in leukemic children (35), including the late development of a syndrome indistinguishable from the "secondary disease" described for rodents. The secondary syndrome was not necessarily lethal; however its development must be considered one of the serious hazards associated with bone marrow transfusions. Recently the British have reported an apparently successful homologous bone marrow transfusion in a patient whose marrow was rendered aplastic with a chemotherapeutic agent (36).

The efficacy or hazard of homologous marrow transfusion thus must be considered incompletely evaluated as yet. However, the evidence is sufficiently

1. Damage to the gastrointestinal epithelium on the basis of agranulocytic or hemorrhagic lesions, rather than on the basis of direct damage to the gastrointestinal epithelium as may be seen in the first few days after exposure, may be seen at this time.

strong to warrant very serious consideration to its use when there is reason to believe that survival will not be possible with functional replacement therapy only. The claim that marrow was efficacious in the Yugoslav accident patients, even when given in the 4th and 5th week, can be taken to indicate that an early decision to give marrow is not necessary, as thought previously from mouse data, and that the decision can be delayed until the need for such therapy is obvious, or until it clearly is not necessary for survival.

Day 15 to 20. As in previous time intervals, no therapy is indicated nor should be given in the absence of severe neutropenia or thrombopenia, or other clearcut indications. Should the necessity for therapy develop, this should be limited to functional replacement therapy. Since recovery is highly probable with this therapy alone, marrow transfusions should be considered seriously only if it is obvious that the patient is failing even with extensive functional replacement therapy.

Day 21-35. If severe neutropenia and thrombopenia is delayed this long, the chances for survival are excellent in the absence of any therapy. Only functional replacement therapy should be considered if necessary except under unexpected extreme circumstances. It is pointed out that minimal evidences of bleeding (microscopic hematuria, scattered petechiae, "pink toothbrush") in themselves do not necessarily call for therapy. However, suitable blood donors should be available at all times, and very careful night and day observation for possible more serious manifestations should be carried out until the peripheral counts are clearly increasing.

No functional replacement therapy was felt to be indicated, nor given in the Marshallese (2), the Oak Ridge individuals (10), or in the Lockport accident

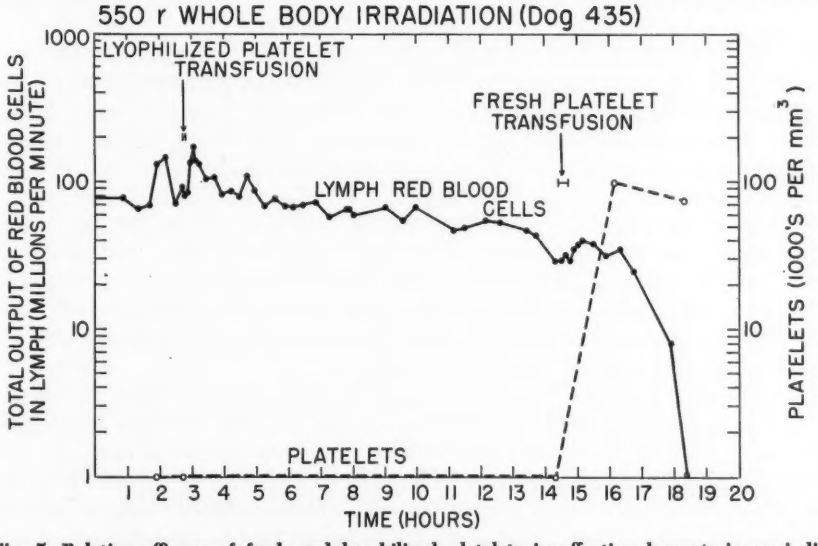
550 r WHOLE BODY IRRADIATION (Dog 435)
LYOPHILIZED PLATELET TRANSFUSION
FRESH PLATELET TRANSFUSION
LYMPH RED BLOOD CELLS
PLATELETS
TOTAL OUTPUT OF RED BLOOD CELLS IN LYMPH (MILLIONS PER MINUTE)
PLATELETS (1000'S PER mm³)
1000
100
10
1
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
TIME (HOURS)

Fig. 5. Relative efficacy of fresh and lyophilized platelets in effecting hemostasis, as indicated by the output of red cells in the thoracic duct lymph of the heavily irradiated hemorrhagic dog. (From Ref. 27).

(15), even though depression of peripheral elements was marked, and in the latter two instances, petechiae and some evidence of infection developed. Thus a "strenuous course of non-intervention" is strongly indicated, unless clearcut indications to the contrary develop.

SPECIAL DIAGNOSTIC PROCEDURES

Bone marrow morphology studies. Although the bone marrow cellularity falls rapidly following total body irradiation in large doses, this fall is of course quite difficult to evaluate in marrow smears. Early (within 24 hours) changes in cell morphology in the bone marrow can be observed easily with careful observation, and such studies would be of considerable diagnostic aid in the hands of one familiar with these changes. The types of abmormality depend on time following exposure, and include pyknosis, chromosome condensation, nuclear fragmentation, chromosome stickiness, chromosome bridges and other abnormal mitotic figures, giant cell formation, and bilobulated cells. The degree to which some of these abnormalities are evident increases with increasing dose; however it is difficult as yet to place quantitative interpretations upon these manifestations. Different portions of the marrow may be affected to different degrees, if radiation has been non-homogeneous.

Mitotic index. Following whole body irradiation, the mitotic index of the marrow (and of other dividing tissues) falls over the first hours and days, and the degree of depression at certain times after exposure is a function of dose (37). The normal mitotic index for human bone marrow is approximately 9 per 1,000 cells, and this has decreased to virtually zero by the fourth day in patients who have received of the order of 200 r or above (11, 19). Thus, serial determination of the mitotic index of the bone marrow allows some estimate of the degree of exposure sustained.

DNA synthesizing cells. Total body irradition affects the number of DNA synthesizing cells both in the bone marrow and in the peripheral blood. The number of DNA synthesizing cells may be determined by use of tritiated thymidine, and autoradiography (38). The changes occur within hours; however, with the autoradiographic technique some days are required before the preparations can be read. Counting of cells is rather a tedious procedure, and the results may not be available until well after the data would be of clinical significance.

Urinary amino acids. Amino acid excretion has been shown by several investigators to be increased following total body irradition, and there is evidence that the newly discovered urinary amino acid, beta-amino-isobutyric acid, may be increased (39). The degree to which determinations of this nature will aid in assessing the severity of exposure remains to be seen.

The above indicated special diagnostic procedures are of value in aiding in the overall evaluation of the patient and in determining the type of management to be used. However, some require rather specialized techniques and knowledge, and considerably more work must be done before any of these approaches can be considered quantitative. The results of such tests at present should be considered in the same light as other diagnostic procedures, namely that they contribute to an overall evaluation of the patient but do not in themselves, individually or collectively, constitute a basis for therapy or prognosis.

ADDITIONAL CONSIDERATIONS

Additional problems arise because of the relative novelty of a severe radiation accident. These include pressures to perform a large number of special studies on the patients (usually studies using blood, by outside groups) and to give therapy of various types to be sure that every possible measure has been taken. Relationships with the press and the public may cause problems.

It is obvious that observations on such patients should be as detailed as possible, to add to our knowledge of the acute radiation syndrome. However, it is equally obvious that patient welfare comes first, and this does not include iatrogenic exsanguination. Therapy should be conservative and pressure to use unproved preparations or procedures must be resisted. A "poly-pharmacy" or "just in case, to avoid criticism" approach has no place in clinical practice. Public information should be handled entirely through a single individual or office. It has been proved repeatedly that the best way to avoid undue publicity and exaggerated rumors, is to give out as much information as feasible, however scanty, and to issue the information truthfully, and as soon as is possible.

DISCUSSION

The above discussion has been oriented mainly around the management of a single, or a few heavily irradiated individuals who can be taken care of adequately with the hospital facilities usually available. It has been shown that the therapy indicated involves no new principles, and simply applies principles well known to physicians with experience in dealing with marrow hypoplasia or aplasia from any source. With vigorous functional replacement therapy, it is felt that human beings may survive a dose of radiation approximately twice that at which they otherwise would die. Such therapy involves, however, constant attention throughout the critical periods, and the use of large amounts of antibiotics and fresh blood when indicated. By use of bone marrow, it may be possible for survival to occur at even higher doses; however the efficacy of bone marrow transplants in human beings has not been adequately evaluated as yet.

It will be apparent that adequate care for even a relatively small number of heavily exposed individuals would tax the facilities of most hospitals. Thus the conditions outlined in the present paper would not be applicable at all under major disaster conditions such as may pertain in the event of nuclear warfare. Thus medical personnel and facilities will not be available for adequate therapy; and many individuals will be without treatment at all, or will have access to aid or treatment given only by themselves, by another lay person, or by individuals with minimal medical knowledge. Thus, while under ideal conditions, a large number of heavily exposed individuals could be saved, these individuals probably would succumb under catastrophic conditions. Also, it would not be possible to conduct those laboratory tests adequately that are of value in diagnosis, and it may be necessary to rely entirely on signs and symptoms, and on dose estimates however crude they may be, for purposes of triage or of prognosis. In the above discussion it has been assumed that thermal or blast injury have not accompanied the radiation exposure. With nuclear warfare, in areas close to the point of detonation, it is probable that large numbers of cases would be compli-

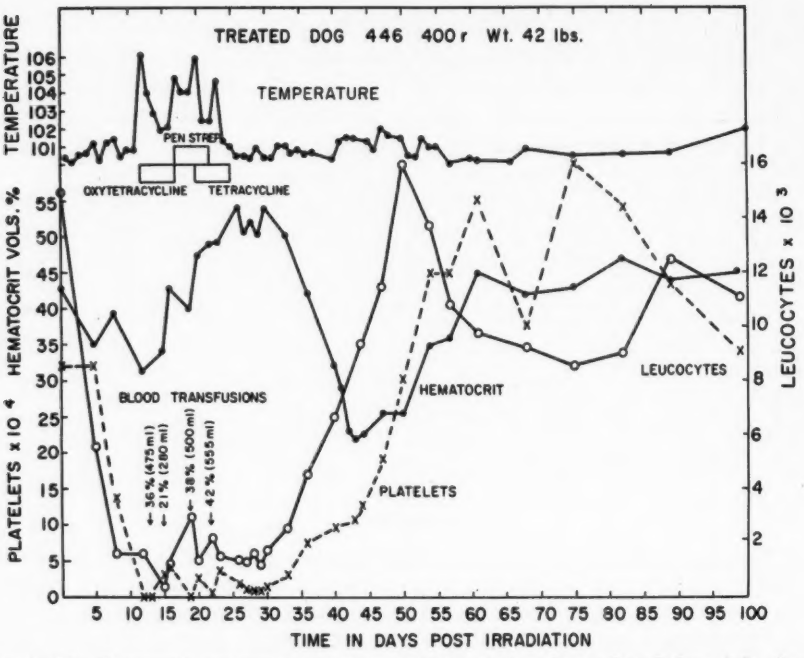

Fig. 6. The therapeutic regimen found to be effective in heavily irradiated dogs (plot from Ref. 33). 400 r is approximately an "LD_{100}" under the exposure conditions employed.

cated by the presence of thermal and blast injury, and the management of these individuals would accordingly be more difficult. In areas affected only by fallout, which may cover literally thousands of square miles and in which doses of the order of several hundred r may be delivered in the course of a few hours to days, it is possible that very large numbers of radiation injuries may be seen, with no thermal or blast injury. In warmer climates in which a minimum of clothing may be worn, and in populations in which decontamination may not be carried out because of ignorance or lack of facilities, it is possible that local lesions to the skin resulting from deposited fallout material may further complicate the acute radiation syndrome.

SUMMARY

The management of the heavily radiated individual has been discussed. There is nothing "mysterious" about the acute radiation syndrome in man, and the manifestations seen are those to be expected in light of the underlying cellular, organ, and physiological changes known to result from the exposure. It is possible, on the basis of signs and symptoms presented and aided to some extent by physical estimates of dose, to place the exposed individual into very broad categories with respect to the severity of exposure, therapy that may be indicated, and prognosis. It is stressed that under no conditions should an individual be treated on the basis of physical estimate of dose, or category, and that therapy should be given an individual only as and when indicated by clinical signs and

symptoms, including laboratory data. Therapy should be on an individual basis always, and should be given when indicated, and not on a prophylactic basis. With severe marrow hypoplasia and depletion of the peripheral blood neutrophils and platelets in the third or fourth week following exposure, it is possible in a high per cent of casualties to tide the patient over with functional replacement therapy involving principally antibiotics and fresh platelets, until individuals' marrow regenerates spontaneously. At higher doses, with complete marrow aplasia and depletion of the peripheral blood elements in the second week or earlier, serious consideration must be given to bone marrow transfusions. The efficacy of this procedure in man has not been established adequately as yet.

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Training for Clinical Use of Radioisotopes: Qualification Courses[1]

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INTRODUCTION

Radioisotopes are established as aids in clinical diagnosis, but the physician has some real obstacles, in the form of specialized training and licensure, before he can use these agents.

The busy physician now demands ways, such as concentrated courses economical to his time, to brush up on scientific progress and to revise his earlier notions on disease and treatment. A desire to be informed and competent in radioisotopes is but one segment of the admirable desire to be abreast of all medical advances. But also we must admit to the element of the "hard sell." Isotope enthusiasts eagerly promote their method in print and at meetings, pharmaceutical companies are quick to seize upon any potential market, and instrument manufacturers fiercely hunt ways to market their products. For a time willing lecturers from the Isotope Division of the Atomic Energy Commission went up and down the land and extolled the wonders of this new tool. Program chairman of various medical assemblies were only too delighted to schedule the newest and the biggest thing. In a word, diverse stimuli send physicians to seek training in isotopes. Hence, diverse motives impose pressures on those who would design and offer courses, and to an extent have dictated the form of some courses. The structure of training courses depends also on the Atomic Energy Act of 1954, which charges the United States Atomic Energy Commission with responsibilities for the licensing of isotope users. As a consequence, the AEC has set up licensing requirements (1).

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GENERAL CONSIDERATIONS

Here we will define certain goals of qualification courses, suggest minimum and desirable elements for training programs, and sample some of the recent efforts to "qualify" isotope users in clinical medicine.

The Goals of Qualification Courses

At least three major goals are common to all training efforts: 1. to meet the AEC requirements for licensure; 2. to acquaint the physician with sufficient knowledge to keep him, his technicians, and his patients from radiation hazard; 3. to use these tools intelligently for reliable laboratory information. Thus we hope that the patient's treatment, where dependent on isotope tests, will be proper and that isotope methods will not fall into disrepute from faulty technique.

No teacher can abdicate his responsibility to define what every student must know before he should practice his art on the public. The AEC's concern is merely for radiological safety. The AEC application form asks for "exposure times" in the training statement. It demands no commitment from the preceptor concerning the competence of the applicant, and at no point is any assessment of competence or knowledgeability made. The teacher, therefore, must be satisfied that the student, the public, and his own teaching reputation are protected.

Necessary Elements for all Training Courses

Each student needs an orderly introduction to six main, sometimes interrelated, areas: 1. Physics. 2. Mathematics and statistics. 3. Methods of instrumentation and measurement. 4. Radiological Safety. 5. Theories of tracer methodology. 6. Medical applications, including indications and contraindications for the tests, and interpretations of results. (Table 1).

TABLE 1. SAMPLE QUALIFICATION COURSES

Course	*Duration*	*Hours*	*Lectures and Films Per Cent*	*Lab. Per Cent*	*Demonst. Clinics etc. Per Cent*	*Misc. Tours etc. Per Cent*	*Diagnosis / Therapy*
A	2 weeks	60	45	28	20	7	x/x
B	2 weeks	80	39	41	20	0	x/x
C	10 days	73	36	47	7	10	x/0
D	8½ days	59	78	8	10	3	x/0
E	3 weeks	115	36	43	14	6	x/0
F	4 weeks	120	23	45	20	12	thyroid
G	*4 weeks*	*147*	49	26	18	7	x/x
	33 weeks	99					
	Basic						
H	6 weeks	214	59	41			x/x
	Clin.						
	10 weeks	409	26	74			

What are the most efficient teaching aids and techniques?

1. Lecture. For some time educators have challenged the formal lecture as a way of teaching. In our experience, too, the lecture, even the best, is an inefficient method of communication and in part is a waste of time. Nevertheless, we persist in giving them and rely on them for certain kinds of introductions to subject matter. Probably as an ideal, the lecture should be replaced with reading assignments followed by a discussion period in the Socratic manner. A planned series of questions and answers would demand fearful intellectual activity by the student, even more on the part of the instructor, and would lead to the illuminated need for further study. This alternate teaching method will be adopted with reluctance, and probably will remain unpopular.

2. *Visual aids.* The U. S. Army Signal Corps films on the *Properties of Radiation* (PMF 5145-B) *and Fundamentals of Radioactivity* (PMF 5145-A) are quite helpful in the animated portrayal of difficult concepts. Motion pictures, slides or diagrams, exhibits, and models all should be energetically exploited. No course will amount to much unless instructors have some inventiveness in this direction. Special devices can be built at moderate cost to enliven some laboratory sessions (Fig. 1).

3. *Demonstrations.* The demonstration lecture, clinic, or variation thereof, is good, particularly as an introduction to active participation.

4. Active laboratory exercise. This is the best and most important part of any intensive training course. The success of the qualification course in radioisotopes will depend on perfection of the laboratory exercises. Here are some criteria for these laboratory sessions: (a) The experiment should be sharp and lively. (b) It should be simple and straightforward to illuminate the concept. (c) Special training devices should be available for many of the topics. (d) The data should raise questions and the student must be challenged to seek the answers. (e) Opportunities for the student to make mistakes should be allowed. He should be encouraged to find them and to interpret them.

Analysis of Several Qualification Training Programs

With no intention of conducting an exhaustive or complete survey, we have sampled schedules from various institutions offering radioisotope courses for physicians. Quimby (2) has published a more inclusive summary of isotope courses. She has defined well some problems of course design, and expressed opinions concerning course standards. The purpose of our sampling was not to find the "average" course, but to detect how wide the spread of opinion might be about an adequate introduction to this field. Table 1 shows how little agreement has been reached on the length, content, and structure of these courses. One advertisement, mailed by a nuclear instrument company to physicians, offered a course in 1959 (not included in Table 1) that stated in part, "This course is carefully planned to exceed the minimum requirements of the USAEC for a license in the use of radioisotopes for diagnostic medicine; yet it is carried out on local area basis *so that only three days need be taken off from the doctor's practice.*" (The italics are mine.) If this is a rational approach to the training problem, then we

are sorely misguided. The courses listed in Table 1 vary from 59 hours to 147 hours, excluding Course H which is a special case. Even some of the shorter ones include therapy. The active laboratory time ranges from 8 to 47 per cent of the total hours, or, including the time devoted to demonstrations or clinics (an intermediate learning approach), from 18 to 65 per cent of the total course time. Note that most courses provide for miscellaneous activities such as tours of isotope laboratories or atomic energy installations, and assistance in interpretation of the AEC licensure application forms.

Evaluation of the Worth of Qualification Courses

A danger exists that we will give overly brief courses because they are easy to present or are most acceptable to the students, rather than ones designed to achieve a well-defined goal. It may be equally unrealistic to set up a period of two to four months as a desirable minimum, even though we suspect that this period of time is closer to the ideal. Therefore we must measure the effectiveness of our training and propose some standards. This is glibly stated, but actually is a hard task. What are some ways of testing? 1. Examination during or after the course. 2. Practical exercises involving calculations, measurement of doses, measurement of samples, and interpretation of results during the course. 3. Distribution of "unknown" standards to be measured in the home laboratory, analogous to the serological samples sent from some state public health laboratories to approved medical laboratories, or to the voluntary "check sample" program of the American Society of Clinical Pathologists. 4. An inspection visit for continuing accreditation. This last might be part of a control system to ensure that safe handling methods are carried out, or could be part of a volunteer system similar to AMA hospital accreditation. Some debate already has begun concerning training standards and quality control in the clinical radioisotope laboratory. Who should set the standards and administer the effort at quality control?

The AEC Division of Licensing makes regular inspections of all isotope licensees, but this is only for considerations of radiological safety. The license makes no measure or requirement of competence. Several states have embarked on licensing programs, but for a variety of reasons these have been opposed by users of radioisotopes.

The program of quality control then reverts to individual institutions involved in training efforts, and to professional organizations concerned with high standards of medical education and practice. The American Board of Radiology now examines candidates in radioisotopes. At its 1959 meeting, the Board of Governors of the College of American Pathologists endorsed "training for pathologists in diagnostic uses of radioisotopes with a view toward ultimate inclusion of such training in the requirements for certification by the American Board of Pathology."

THE ORINS MEDICAL DIVISION COURSE FOR AEC QUALIFICATION

At the present time the Medical Division of ORINS offers what we regard as a minimal preparatory course for a physician who wishes to use diagnostic radioisotopes. Three one-week sessions are separated by one or two months. This permits the physician to be away from his work for shorter periods of time and the interval makes it possible for him to assimilate and review some of the material of the course. During the first two weeks basic subjects are emphasized, while the third week is devoted primarily to the clinical use of six of the most common and widely accepted diagnostic isotope procedures. (See Table 2).

Following is a brief summary of the principal laboratory exercises for Preclinical I and II:

TABLE 2. CURRICULUM OF MEDICAL DIVISION, ORINS—3 WEEK[a] QUALIFICATION COURSE

Preclinical I and II (2 weeks)	*Lectures, Films*	*Demonstration*	*Labs*	*Total Hours*
Basic Physics	9	1	3	13
Mathematics and Statistics	1	1	2	4
Instrumentation and Measurement	10	4	21	35
Radiological Safety	4	1	2	7
Tracer Methodology	3	3	10	16
Miscellaneous Other	4	1	—	5
Total Hours	31	11	38	80
Clinical (one week)				
Thyroid Function	5	2	6	13
Chromium-51 Red Cell Label	2	1	3	6
Iron-59 Utilization	1	1	3	5
Iodine-131 Albumin Plasma Volume	1	—	3	4
Iodine-131 Triolein Absorption	1	—	2	3
Cobalt-60 Vitamin B-12 Absorption	1	—	2	3
Miscellaneous	5	—	—	5
Total Hours	16	4	19	39

a. Given as 3 separate weeks.

Note: The allocation of time is partly artificial. Basic Physics is also presented in Instrumentation and Measurement; mathematics and Radiological Safety appear in nearly every laboratory session. Other topics overlap, too.

Preclinical I (First week)

1. *Basic physics.* Measurements are made of a low-energy gamma emitter, a high-energy gamma emitter, and a beta emitter with scintillation and GM detectors and with cardboard, plastic, and lead filters. Measurements are made at various distances from the detector to the source to plot the measured radioactivity and observe the inverse square law.
2. *Statistics.* The basic training aid is a statistics board (Fig. 2) into which can be fed from a reservoir varying numbers of steel beads; such things as the distortion of a distribution with blunders or skewed distributions are shown. The student is introduced to the concept of statistical errors in random events by multiple individual counting of low-level radiation sources.

3 and 4. *Electronics.* Students learn to construct circuits on an "electronic breadboard" (Fig. 3) that demonstrates such electronic functions as rectification, transformation, and amplification, and culminates in a complete working Geiger-Muller counter. Various electronic components are demonstrated and their essential function is explained (3).

5. *Decay and interaction.* From a simple ion exchange column (Fig. 4) containing a small amount of cesium-137, the radioactive daughter barium-137m

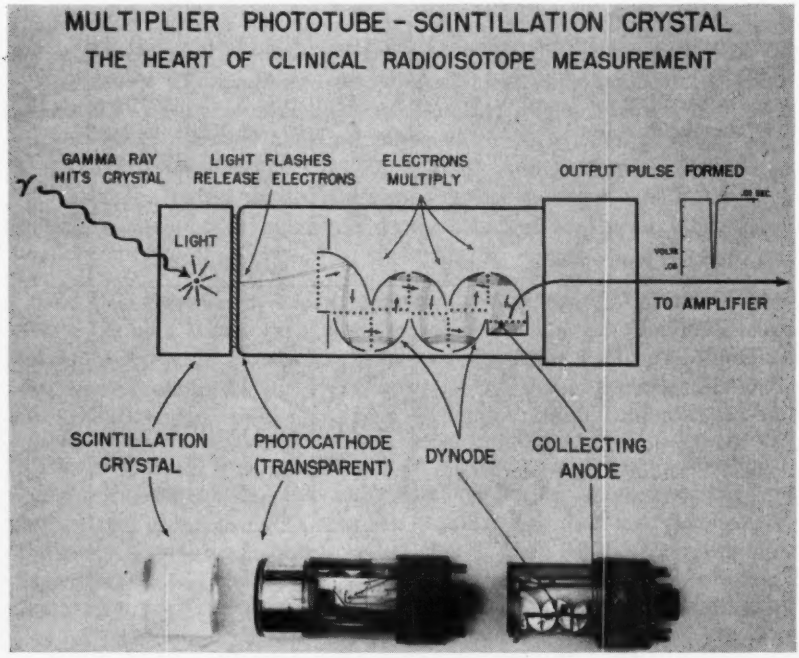

Fig. 1. Expended photomultiplier tubes have been dissected and mounted with a diagram in the training laboratory in order to remove some of the mystery surrounding counting equipment. Ordinarily encased in lead shielding, it is often never seen by physicians.

is separated. The very short half life of the barium isotope can be plotted during one laboratory session. At the same time the build-up to equilibrium of the parent and daughter is measured (4). Students during this exercise also show attenuation of cobalt-60 gamma rays by lead, thereby demonstrating the similarity between half life and half value layer, and are introduced to the principles of radiation sheilding.

6. *Specific activity and isotope dilution (5).* As a first introduction to tracer methodology and biological systems, the experiment has been designed to show the dependency of results obtained with radioisotope tracers on the dimension of the compartment that is traced. Goldfish in different pools that contain the same amount of radiosodium chloride but sharply graded concentrations of total sodium chloride show distinct differences in the amount of radiosodium removed from the pool. A simple isotope dilution exercise is also carried out to find the volume of a pool of unknown size.
7. *Basic considerations of gamma counting.* The factors that influence a counter's efficiency are shown in an experiment using a scintillation counter, filters or absorbers, and scattering media. The basis for measuring energy peaks in the gamma spectrum is also introduced (6).

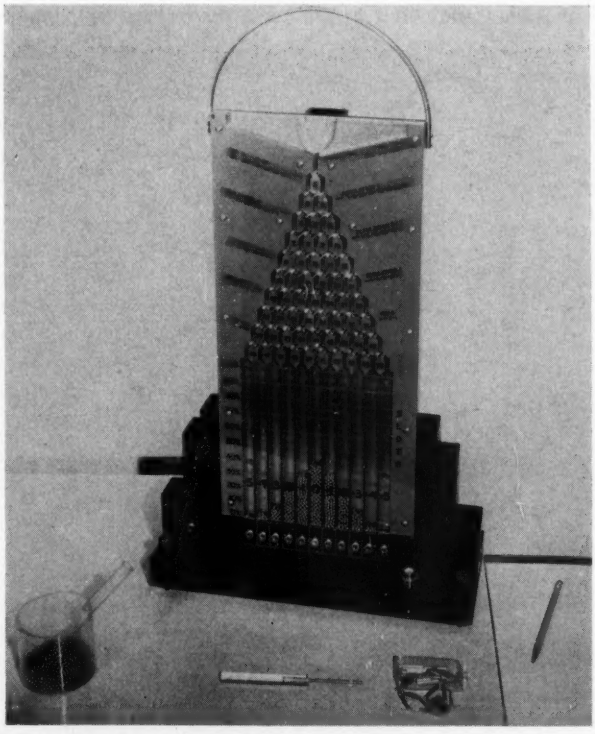

Fig. 2. An apparatus for studying random distribution of varying sized samples. It is applied effectively to counting problems in measuring radioactivity.

8. *Autoradiography.* Gross autoradiograms are made from animal tissues previously prepared by injection of a suitable isotope. Students also examine by direct microscopy a variety of microscopic autoradiograms.
9. *Sensitivity.* Measurements are made on three different isotope sources. The students use three detectors: the Geiger-Muller tube; sodium-iodide crystal with threshold set at 50 kev; and sodium-iodide crystal with threshold set at 250 kev. In this exercise the student sees the effect of variation in distance of the source from the detector; differences in count rate produced by sources of different intensity; difference in count rate caused by the size of the detector, the energy of the emission, and type of emission; and the difference in response caused by the threshold setting of the detector.
10. *Biological application.* The students follow the kinetics of a biochemical reaction occurring in actively growing yeast cells by finding the biological half time for the incorporation of phosphorus-32 into yeast cells. In a separate exercise the labeling of erythrocytes *(in vitro)* with radioactive chromium is carried out and plotted as a function of time.

Preclinical II (2nd week)

1. *Beta counting.* With a Geiger-Muller tube as the detector, the effect of

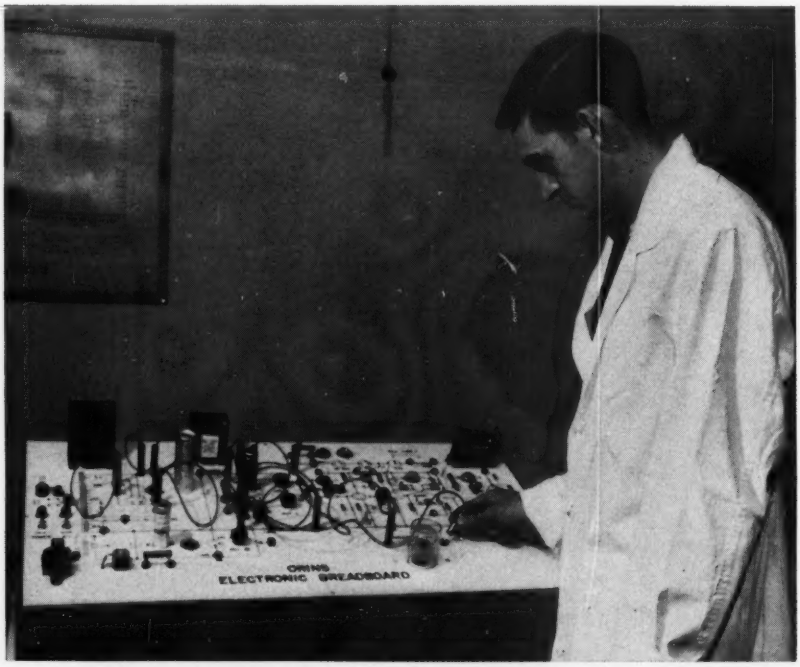

Fig. 3. This "breadboard" orients physicians to the language and principles of electronics, but the one-day laboratory does not guarantee to make skilled repairmen of physicians. (Plans are available for do-it-yourself construction.)

geometry, energy, absorbers, and coincidence loss on the observed counting rate is found. In a second part of this experiment, with a simplified approach, the student estimates the absolute amount of radioactive isotope present in a beta-emitting source.

2. *Gamma counting.* The session is designed to acquaint the student with a number of different instruments that may be used to measure or detect gamma rays. Appropriate measurements are made on the following instruments: well-scintillation counter, external scintillation counter, end-window GM tube, high-pressure ionization chamber, and electroscope. In each of these measurements stress is placed on 1. geometry, 2. relative sensitivity, 3. linearity of response, and 4. the interrelationship of these factors.
3. *Survey and monitor.* Roentgens per hour from a radioactive source are measured with a variety of monitor and survey instruments including pocket dosimeters, direct reading electroscope, and assorted survey meters. Film-badge dosimeters are also examined and density readings are made.
4. *External counting.* External measurements of the percentage of uptake are performed on standards and on prepared manikins that contain unknown amounts of mock-iodine in the thyroid region and dispersed amounts of isotope throughout the manikin to represent body background (Fig. 5). Measurements are made with a variety of detectors including end-window GM counter, collimated scintillation crystal, low-threshold crystal detector, medical spectrometer, and a side-window bismuth-wall GM counter, pointing up the difficulties of precise external counting.
5. *Field of vision.* The isoresponse curves for a radioactive source placed in front of a collimated crystal are mapped out. Changes produced when the source is measured in water are also plotted, and the modifications of these two isoresponse maps achieved by measuring above 250 kev threshold are also determined.
6. *Biological procedures: Apparent Blood Volume and Urinary Excretion.* Dogs are injected with four different isotopes: iodinated serum albumin, sodium chromate (chromium-51), iron-59, and colloidal gold-198. Principles of biological space measurements are thereby introduced. The disappearance times from the blood are determined and "apparent blood volumes" are calculated. Urinary excretions are concurrently measured.
7. *Radiological safety.* Autopsies are performed on the dogs used in Experiment 6 to provide experience in radioactive autopsy techniques. Radiation safety precautions are followed. The sequence of the autopsy is altered to accommodate the collection of proper samples for radioassay. (Exercises in health physics are a part of all the laboratory sessions.)
8. *Radioisotope distribution studies.* This is a continuation of Experiments 6 and 7. From the animals used in the previous experiments selected organs and fluids are assayed and autoradiographic correlations are made from these same tissues.
9. *Field trip.* The class tours a reactor facility to see isotope production. An opportunity is also provided to visit a local radiopharmaceutical production laboratory.

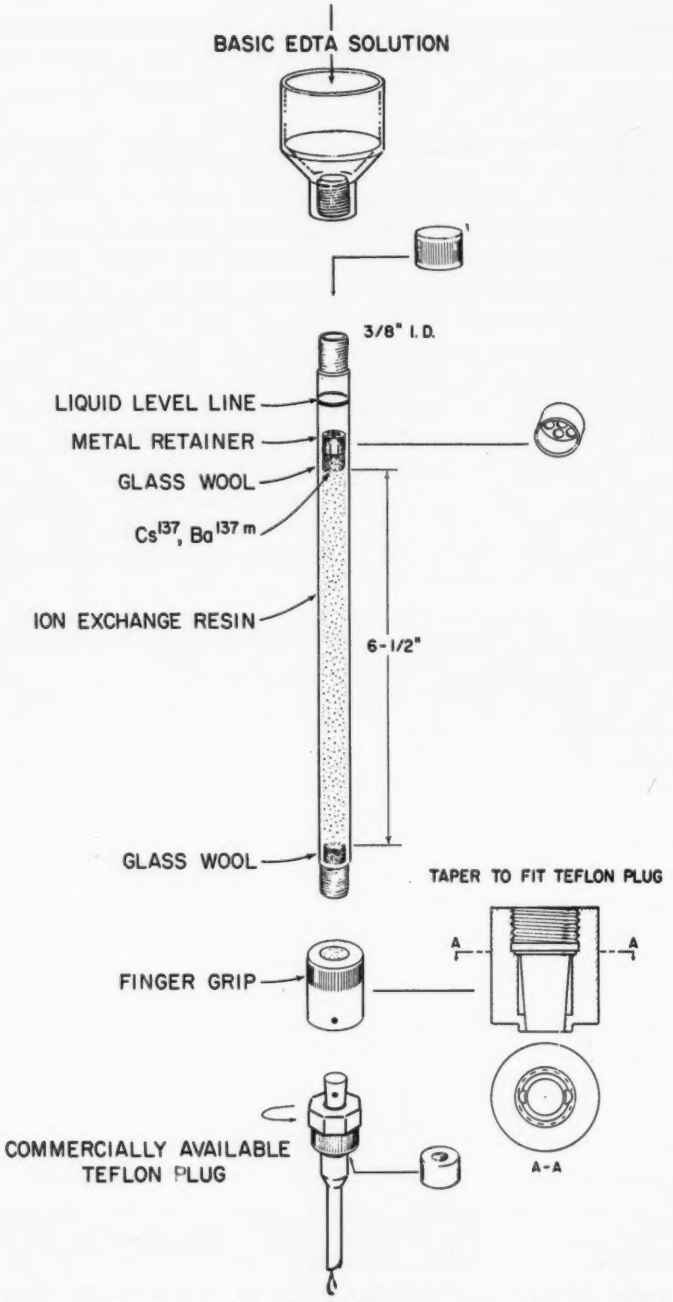

Fig. 4. Diagram of parts and assembly of a half-life demonstrator. It can be constructed in any laboratory shoproom. (Directions for construction and for the laboratory exercise can be obtained from Dr. R. L. Hayes, ORINS.)

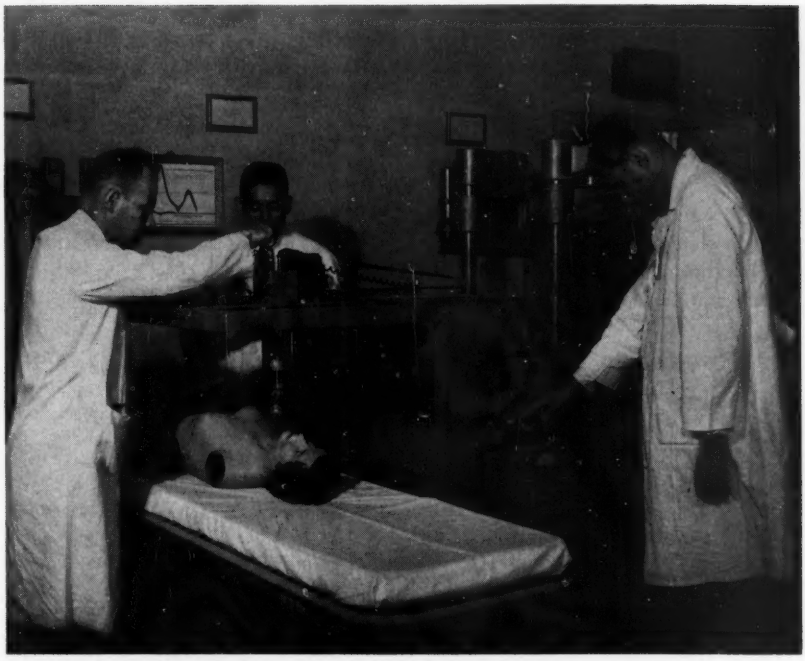

Fig. 5. Manikins containing mock-iodine "thyroid glands," with unknown percentage of uptakes and body background activities, originally constructed for a thyroid uptake calibration survey, have been used repeatedly as training aids. Skill in external measurements and facility in scanning are acquired in the absence of live patients.

Clinical (Pathology) Week.

The third, or clinical, week is devoted to performing on human subjects specific isotope tests. Explanatory lectures and demonstrations are interspersed into these sessions of active clinical measurements. A major emphasis is given to thyroid uptake tests. Measurements are made on a variety of instruments so that the participants can see for themselves the wide range of answers that might be obtained by using identical standards and patients but different detection systems. Chromium-51 is used as a red cell label to determine survival time and red cell mass. Iron-59 is given for erythrokinetic and oral iron absorption studies. Cobalt-60 labeled Vitamin B_{12} absorption and urinary excretion tests are also presented. The participants also determine plasma volumes by using iodinated human serum albumin, and estimate fat absorption by measuring blood levels and fecal excretions following oral doses of iodine-131 labeled triolein. Although some information is given about other iodine-labeled compounds, such as Rose Bengal, or Diodrast, and information is also offered in circulation and cardiac output studies or determinations of graft viability, actual clinical experience of these additional procedures is not possible owing to the limited time.

Although some scanning procedures are demonstrated on patients who have had therapeutic isotopes, we strongly emphasize that this course is not designed to offer any kind of credit toward approval for therapeutic uses of radioisotopes.

SUMMARY

Courses to meet AEC requirements for medical uses of radioisotopes vary widely in content, structure, and length. Some goals, and some minimum and desirable elements for courses have been proposed. In the three-week course given by the Medical Division of ORINS, special training aids have enlivened the presentation of difficult basic information to physicians.

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The ORINS Linear Scanner in Diagnosis and Treatment of Thyroid Carcinoma With Iodine^{131}*

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Oak Ridge

INTRODUCTION

The development of radioisotope technique and the improvement of instruments have made scanning a very popular diagnostic procedure. There are several methods of scanning. One technique uses a radiation detector that scrutinizes an object for the presence of radioactivity within the object; we call it probe scanning, and it is used by surgeons in thyroid and brain operations. Another technique in effect produces an image of a radiation-emitting area through a detector connected to a mechanical printing device. It is the most widely used technique, and we shall refer to it as "area scanning." Both techniques provide useful information in regard to localization of activity, but none in regard to its quantity. Ways and means that will give us this quantitative information have to be found, because the dosimetry of internal radiation (for which a practical method is not available) depends upon this factor. We think that linear scanning might be one of the ways to solve this problem. Essentially, it is a method by which a continuous recording of count rate is obtained by moving radiation detectors along the body, producing a curve in which every point on the curve represents count rate versus position in the long axis of the body. In other words, it draws a profile of radioactivity present in an object or in a patient's body.

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*Work done at the Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee, under contract with the United States Atomic Energy Commission.

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Corbett, *et al* in England were the first to publish on linear scanning. They used a Geiger-Muller tube and called the method "profile scanning" (1). Concannon and Bolhuis of Chicago modified the technique by using a scintillation detector with a collimated head that had a wedge-shaped slit (2). Both groups have proved the clinical value of linear scanning in diagnosis and treatment of well-differentiated thyroid carcinoma (3). The purpose of this paper is to introduce a new type of linear scanner, to determine whether or not an improvement of the method has been accomplished with this Oak Ridge Institute of Nuclear Studies (ORINS) linear scanner, and to define its clinical validity.

METHOD

The instrument (Fig. 2) has 12 scintillation probes, each equipped with a two-inch sodium iodide crystal. The probes are mounted linearly in two units, six in each, between collimating lead lips two inches thick. The crystals face each other in a vertical plane, which is perpendicular and transverse to a table on which the patient is positioned. This table is motor driven and moves between these two detector units at a constant speed. Each one of the crystals is attached to a photomultiplier tube with a modified preamplifier. All twelve probes are connected to one medical spectrometer, which has a recorder attached.

All linear scans were performed with the patient in a supine position. The table speed was ten inches per minute, while the recorder speed was set at one inch per minute, so that the scale of patient to scan is ten to one. Certain land-

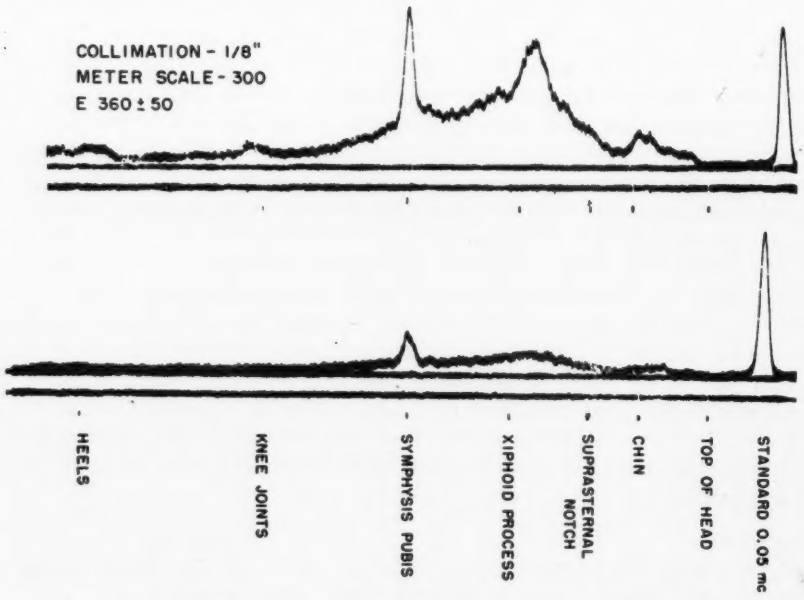

Fig. 1. Linear whole body scans 24 and 48 hours after oral administration of I^{131} to a patient without evidence of functioning thyroid tissue.

marks were recorded on the scans throughout the study by means of automatic microswitches, which were set before the test (Fig. 1). The setting on the spectrometer varied according to the dose and to the isotope administered. For the iodine-131 studies, the spectrometer was set at 360 kev, with a window width ranging between 20 and 100. The collimator opening was set at 1/16th of an inch to 1 inch, as demanded by the situation. Another variable was the scale selector of the rate meter. A standard was also used. It consisted of a cylindric bar, filled with 50 microcuries of mock-iodine, and placed across the table at the head or foot of the patient. The machine was originated by M. Brucer, designed by D. Ross and A. C. Morris, Jr., all of the Medical Division of the Oak Ridge Institute of Nuclear Studies (ORINS), with the assistance of J. E. Francis and C. C. Harris of the Oak Ridge National Laboratories (ORNL), and it was built in the ORINS shop (4).

This study was conducted at the Medical Division of the Oak Ridge Institute of Nuclear Studies over a period of five months (5). Linear scans were made of every suitable patient who had received a radioactive isotope in the process of diagnosis or treatment or both. Ten radioisotopes and an additional four radioiodinated compounds were studied in 49 patients. Twenty of these 49 patients on whom this report is based had thyroid carcinoma and had received iodine-131 in doses ranging from 0.5 to 160 millicuries.

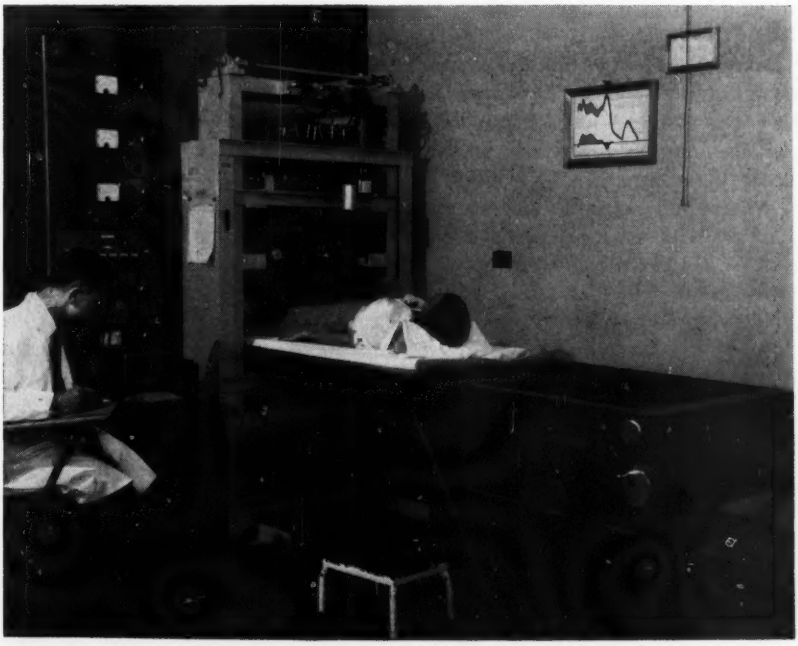

Fig. 2. The ORINS linear scanner.

RESULTS

The case reports of 6 of these 20 patients are presented here.

Case No. 1.

Diagnosis: Follicular carcinoma of the thyroid gland.

The diagnosis was made as a result of a cervical node biopsy, which was followed by a total thyroidectomy and, in the course of treatment by two more surgical neck explorations, each time with removal of masses of lymph nodes. Figure 3 shows a linear scan three days after the administration of a test dose of 5 millicuries of iodine-131. Two areas in this scan are suggestive of metastases, one just below the suprasternal notch, representing iodine uptake in the lymph nodes in the upper mediastinum as confirmed by an area scan and known to be present by extension of the surgical neck exploration into the substernal area. The other metastasis is located 3.5 cm above the xiphoid process. Posterior-anterior area scans at this level revealed uptake on both sides of the dorsal spine. These metastases had not been demonstrated before.

Case No. 2.

Diagnosis: Follicular carcinoma of the thyroid gland with metastases to regional and mediastinal lymph nodes and invasion of the larynx.

The patient had a sub-total thyroidectomy in 1949 for a thyroid nodule, and a second one for a recurrence in 1950, which was followed by total removal of the thyroid gland, a left radical neck dissection, and resection of nodes from the mediastinum because carcinoma had been found at the time of her second subtotal thyroidectomy. In the following years her checkups were negative until 1957 when uptake of iodine-131 reappeared in her neck. Figure 4 shows a series of four scans made 1, 2, 3, and 6 days after administration of 99.8 millicuries of iodine-131. The activity throughout the whole body falls off promptly except for two prominent areas where activity remains elevated: the first, just above and below the suprasternal notch and the second just below the umbilicus. These two areas were scanned with a conventional scanner. The uptake over the suprasternal notch was identified as iodine-131 retention in the neck outside the thyroid bed, representing lymphnode metastases in the lower part of the left cervical chain and in the upper part of the mediastinum. The peak just below the umbilicus in the linear scan was identified as a metastatic lesion in the area of the right iliac bone next to the sacroiliac junction. It should be mentioned that the patient had had pains in her right hip, with limitation of motion in the lumbosacral spine, for about nine months before this study. X-ray surveys of the bones of this area had been reported as negative on several occasions. This figure also shows the effect of variations in window width and meter scale on the count rate, reflected in the variations of the area of the standard with its constant activity.

Case No. 3.

Diagnosis: Follicular and papillary carcinoma of the thyroid gland.

The patient had a total thyroidectomy and a modified neck dissection on the left in 1958, and three surgical neck explorations in 1958 and 1959. Because of the persistence of uptake in her neck, she received 98 millicuries of iodine-131. Figure 5 shows a series of scans obtained at 24-hour intervals for four consecutive days. It is worth mentioning that the profile of a low neck count is maintained throughout the second day. Not until the third day did the uptake in the neck become prominent. An area scan of the patient's neck showed uptake of iodine-131 in three different levels comparable to the group of three profile peaks in the neck area on the linear scan of the same day.

Case No. 4.

Diagnosis: Follicular carcinoma of the thyroid gland in Graves' disease.

The patient had a subtotal thyroidectomy in 1953, followed by a total thyroidectomy and a radical neck dissection on the left. Residual uptake in the area of the thyroid bed was ablated with 30 millicuries of iodine-131. Figure 6 shows a series of four linear scans with persistent and prominent elevations of count rate at the level of the maxilla and mandibula and at the level of the umbilicus, the former representing iodine-131 in the nasal secretion and the saliva, the latter iodine-131 in the intestines. It is interesting to notice that the activity in the nose is maintained longer than in the saliva and that an appreciable amount of iodine-131 is apparently handled by the gastrointestinal tract of this patient.

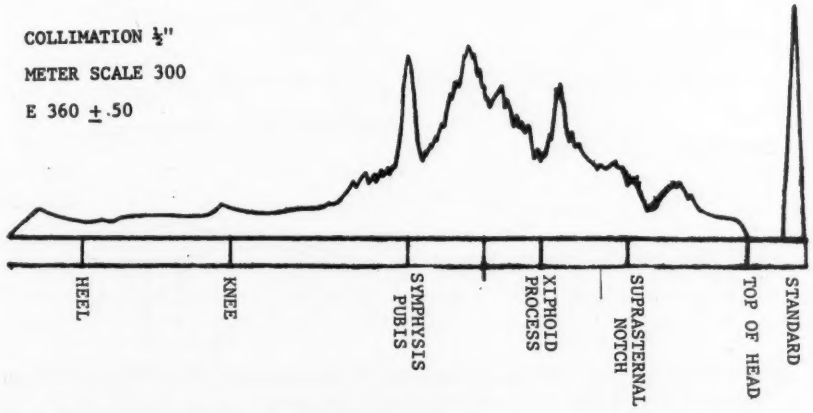

Fig. 3. Three-day scan from a patient with thyroid carcinoma metastatic to the lungs.

Case No. 5.

Diagnosis: Alveolar carcinoma of the thyroid in a large goiter, with marked substernal extension and obstruction of the right supraclavicular vein; congestive heart failure.

Very little history is available on this patient. She was started on iodine-131 treatment, with an initial dose of 30 millicuries. Subsequently she received 490 additional millicuries in fractionated doses over a period of ten months. At her last admission she was improved. Figure 7 represents two scans taken one and six days after the administration of 150 millicuries of iodine-131. It is a very unusual 24-hour scan because of pronounced retention of iodine-131 throughout the whole body. This probably is related to fluid retention due to congestive heart failure. The second scan superimposed on the 24-hour scan shows dramatic changes: Prominent uptake remains at the level of the suprasternal notch, representing uptake in the patient's goiter, while the activity in the rest of the body had subsided, demonstrating the beneficial effect of bed rest and proper administration of digitalis and diuretics.

Case No. 6.

Diagnosis. Adenocarcinoma of the thyroid, predominantly follicular; metastasis to regional lymph nodes, both lower lung fields, right sixth rib anteriorly, and second lumbar vertebra.

The patient had a subtotal thyroidectomy in 1953, with removal of a nodule

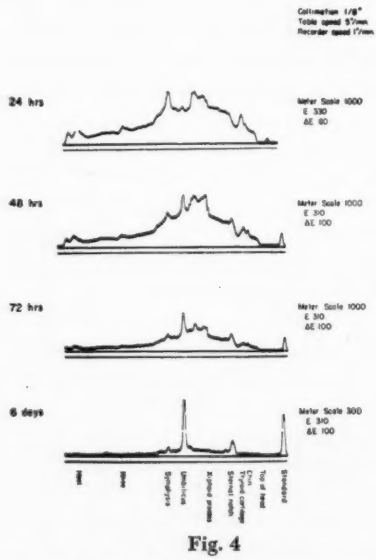

Fig. 4

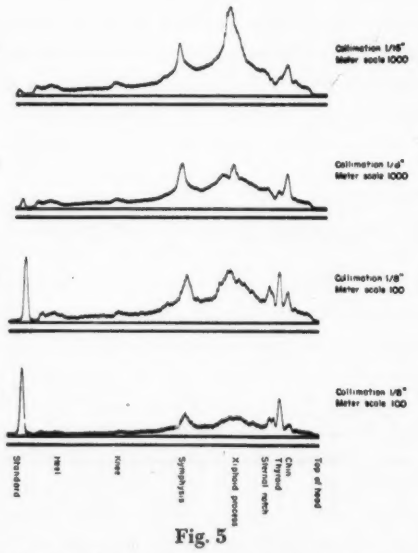

Fig. 5

Fig. 4. Series of four scans from a patient with thyroid carcinoma metastatic to cervical and mediastinal lymph nodes and to the right iliac bone.

Fig. 5. Series of four scans from a patient with thyroid carcinoma metastatic to cervical lymph nodes. (Scan for second day collimation is ⅛″)

harboring carcinoma. Five months later he was found to have collapse of his second lumbar vertebra and a metastatic tumor in the right sixth rib anteriorly. Subsequently, he had a total thyroidectomy followed by external radiation. Shortly thereafter multiple nodular lesions in both lower lung fields appeared. From then on he was treated with 3 grains of desiccated thyroid a day until June 1958. Since that time he has had 368 millicuries of iodine-131 divided in three doses. Figure 8 shows two scans taken one day and nine days after a treatment dose of 157 millicuries of iodine-131. The one-day scan shows seven distinct rises in activity, namely, at the level of the maxilla and mandibula, representing iodine-131 in the nasal secretion, in the saliva of the oral cavity, and in the salivary glands; at the level of the thyroid cartilage, representing uptake in the region of the left superior pole of the thyroid gland; between the suprasternal notch and two centimeters below the xiphoid process, representing uptake in the right paramediastinal area, left hilus, both lower lung fields, and in the sixth right rib; next to it, just above the umbilicus, the isoceles peak was identified with the metastasis in the second lumbar vertebra, and a similar peak just above the symphysis pubis represented iodine-131 in the urine present in the bladder. These five areas of uptake were documented by conventional area scans and X-rays. The remaining two areas of rise in activity at the level of the knee joint and the foot are unexplained so far, and attempts to identify the organs of iodine-131 retention by area scan have failed, as has an aspiration of a knee joint. The second scan, at nine days, demonstrates the over-all loss of activity, with the very marked preservation of uptake in the areas infested by metastases.

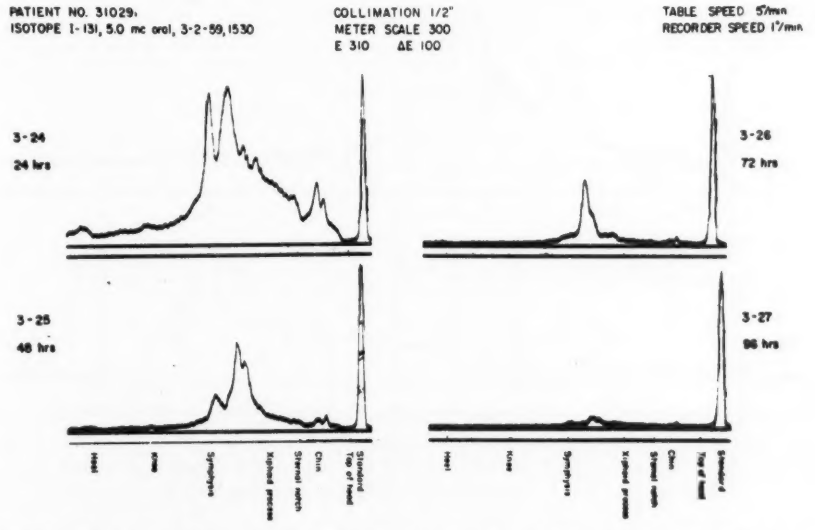

Fig. 6. Series of four linear scans of a patient showing sites of "physiological" elimination of I^{131} in nasal secretion and intestinal contents.

DISCUSSION

From these results we have made the following observations about the ORINS linear scanner and its validity for clinical work:

1. A linear scan profiles the distribution of iodine-131 throughout the whole body of a patient in one single test by recording the different levels of activity along the longitudinal axis of the patient.

2. The time required for the whole body scan is ten minutes. This makes the linear scanner a practical instrument for screening patients for metastases from a well-differentiated thyroid carcinoma.

3. Concentrations of iodine-131 can be distinguished as to their level on the long axis of the patient even in close proximity, indicating a satisfactory resolution factor.

4. Linear scanning essentially is an *in vivo* study, with all the advantages of such a method. For example, it facilitates recognition of complications such as variations in mode of excretion, incidental retention of iodine-131 and others, and can so decrease the potential hazards of large treatment doses.

5. All these features of the instrument refer to its localizing properties. The more important quality, however, is its potential for quantitative exploitation of the scans. A number of different ways have been explored in this matter:

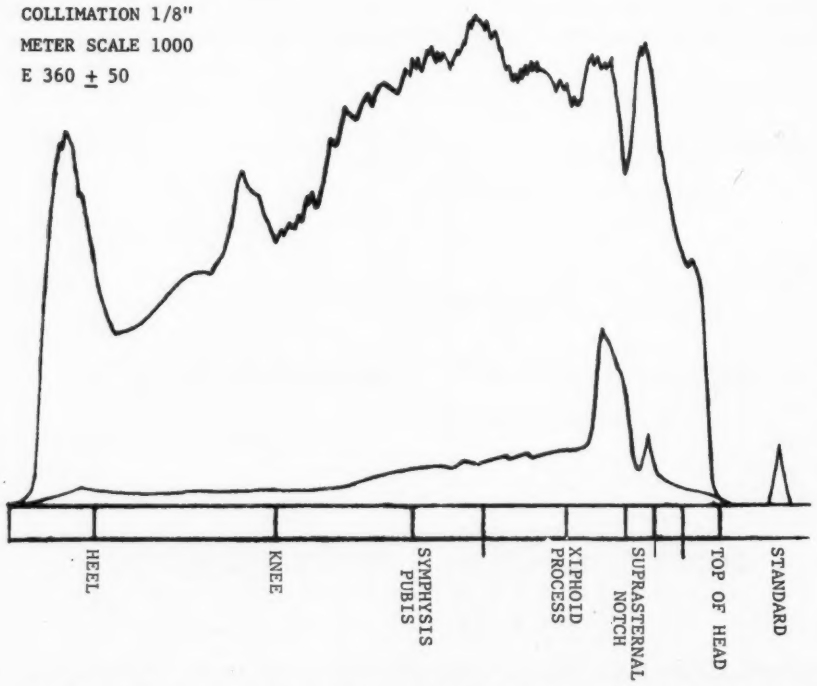

Fig. 7. One and 6-day scans of a patient with thyroid carcinoma in a large goiter with substernal extension who also had peripheral edema and congestive failure.

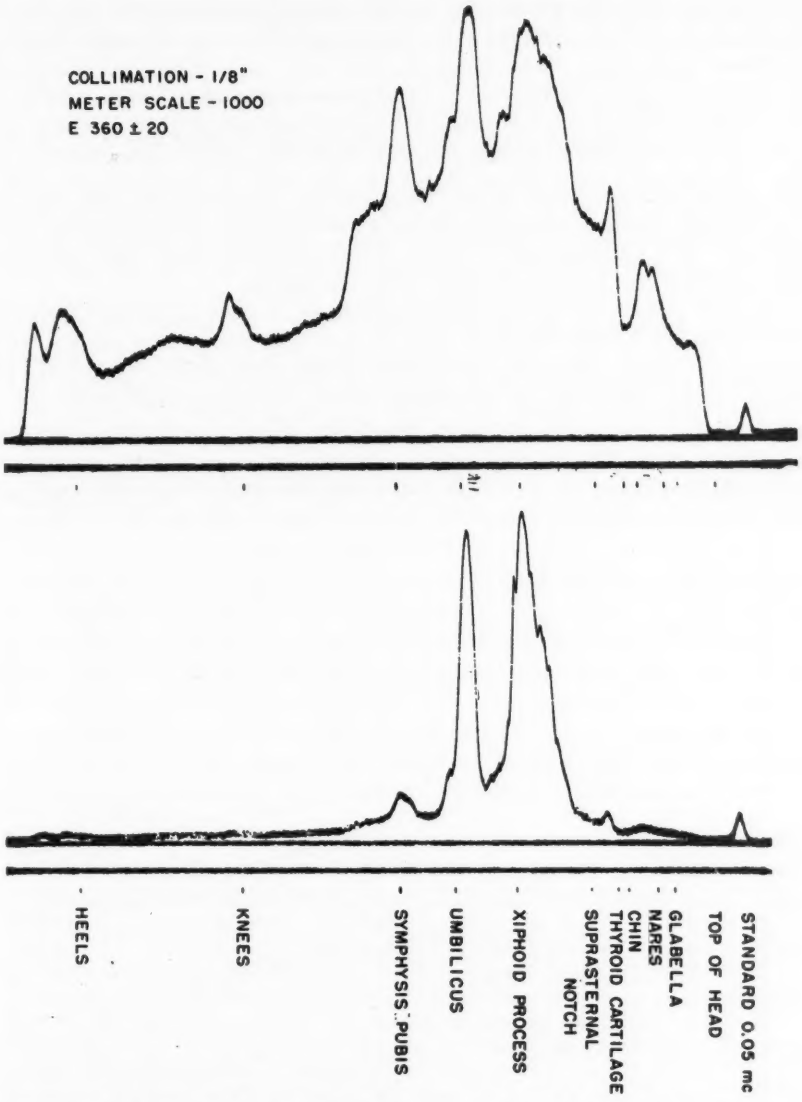

Fig. 8. One-day (top) and 9-day scan (bottom) from a patient with thyroid carcinoma metastatic to regional and mediastinal lymph nodes, to both lower lung fields, to the right sixth rib anteriorly and second lumbar vertebra.

a. The standard with its known constant activity of 0.05 millicuries of mock-iodine was used as a quantitative reference. An attempt was made to correlate the total area under the scan, or any desired part of it, with the area representing the standard, and to calculate the unknown activity, Ax, with the following equation:

$$\frac{\text{Ax}}{\text{0.05 millicuries}} = \frac{\text{Area under the scan}}{\text{Area under the standard}}$$

The calculated values were all low and obviously erroneous, for good reasons: This method requires a standard reference phantom that would meet the characteristics of the human body, which varies constantly from cross section to cross section in one body, and from patient to patient.

b. The calculation of uptake in metastases was attempted by using the whole body activity represented by the total area under the scan as a quantitative reference (Case 6, Figure 8). This method does not require a phantom, but uptake in one area expressed in percentage of whole body activity is not of great practical value. It is uptake in percentage of the administered dose that we want to know. This information can be obtained if a sufficient number of early scans (such as 3, 6, 12, and 24 hours after administration of the dose) are made because a plotting of the areas of these scans would permit a sufficiently

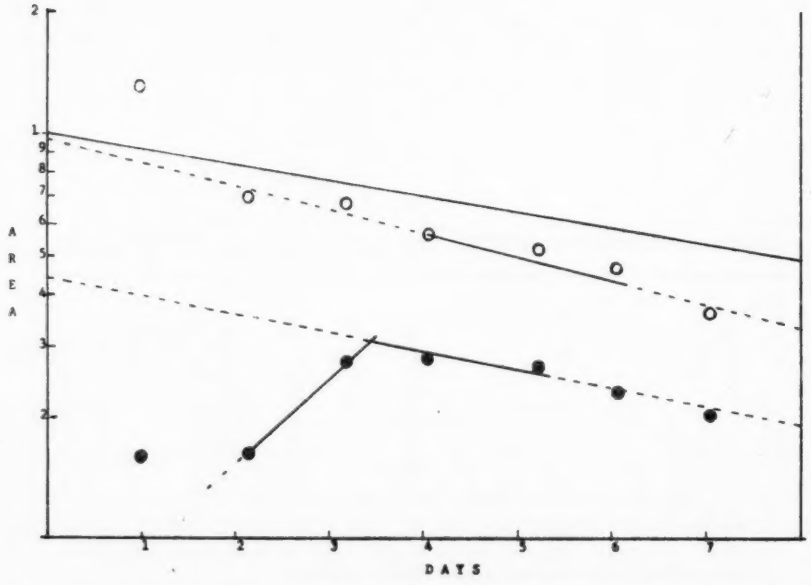

Fig. 9. Effective half life of I^{131} in the metastases (o) (5.9 days) and in the whole body (●) (5.1 days) of a patient whose scans are shown in Fig. 8. The graph also shows the rate of uptake and the time of maximum uptake of I^{131} in the metastases. For comparison the physical half life of I^{131} has been graphed also (top curve).

accurate back extrapolation to zero time, which would determine the area at zero time, which in turn should be equivalent to the administered dose.

c. A third possibility of quantitation is the determination of effective half life in the tissue. To accomplish this, a series of scans must be obtained. If one then plots the areas of these scans that are attributable to metastases or organs versus time after addministration of the dose, a curve results (Fig. 9) that represents rate of uptake in the metastasis or organ, time of maximum uptake, and rate of reduction of activity in tissue, which in essence is effective half life, that is the time at which a 50 per cent reduction in activity has occurred. The difficulty here, however, is the decision of how much in a scan can be attributed to the metastasis. This is arbitrary so far, and explains the somewhat high value of 5.9 days effective half life in a metastasis as compared to the average value in a normal thyroid gland which is an estimated 6 days (Fig. 9). Pochin (3) too has found effective half lives of iodine-131 in metastases from well-differentiated thyroid carcinomas as long as 6 days.

d. The discussion on quantitation should not be closed without mentioning that the instrument can be used as a whole-body counter. Naturally, it cannot do the job of a whole-body counter, but total body counts have been used with reasonable results in determination of effective half lives of iodine-131 in therapeutic doses.

CONCLUSIONS

The linear scanner has demonstrated usefulness in the diagnosis and treatment of thyroid carcinoma. It may fill a gap that exists in nuclear instrumentation between the conventional methods of scanning and uptake measurements on the one hand, and whole-body counting, on the other. It profiles the activity within the patient, it scans the whole body in ten minutes, and it offers quantitative information. The accuracy of this quantitative information cannot be defined on the basis of the little evidence presented here. It is probable that the method can be made quantitative, however, and aid in further development of dosimetry of internal radiation.

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The Use of the Counting Rate Profile in Radioisotope Scanning Techniques

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Cleveland

INTRODUCTION

In the application of the automatic scintillation scanner for the visualization of large organs by means of deposited radioactivity, one of the primary problems is the differentiation of small variations in counting rate between the site of interest and its surrounding environment. In many cases this difference is sufficiently small so that such distinction has not been readily observable. For this reason, attempts have been made to accentuate such differences by means of various non-linear recording devices. These systems have fallen into two forms: the first method involves the use of a counting rate controlled cut-off circuit in which the printing mechanism of the scanner is activated only over areas exceeding a preselected counting rate (1, 2, 3). This system produces an infinite contrast between zero recording below the counting rate cut-off, and a proportional response above the counting rate cut-off. The second type of non-linear recording is based upon the logarithmic response of film density to light (4, 5, 6). Depending upon the degree of accentuation desired, it is possible to obtain a ten-fold increase of density with only a 30 per cent increase in counting rate (5).

The disadvantages of these accentuation techniques are two-fold: first, in the counting rate controlled technique no record is obtained from any areas with radioactive deposition below the counting rate cut-off level; no data are obtained on what actual variations exist in these regions. Secondly, in the light recording methods, the sharp accentuation with counting rate is likely to reach a density saturation over a short counting rate range, so that information over all areas both above and below this range is lost (6).

From: Radioisotope Laboratory, Highland View Hospital.

Presented at the Sixth Annual Meeting of the Society of Nuclear Medicine, Chicago, Illinois, June 17-19, 1959.

The use of either of these accentuation techniques is entirely dependent upon accurate representation of the counting rate variation. In addition, it has been found not only desirable, but necessary to record multiple scannograms at various accentuation or cut-off levels. This is not because the entire counting rate cannot be recorded over one range, but because accentuation must be matched to widely differing counting rate levels for maximum differentiation. For example, the identification of counting rate variations of 20 per cent in the right thicker lobe of the liver might involve accentuation levels considerably different from levels in the thinner left lobe of the liver. Thus, two or more ranges of accentuation would be required for complete visualization of the whole organ. For this reason, it has been necessary to accurately measure and record the linear scan or "liver profile" for variations of counting rate during excursions of the detector over the body surface. The profiles are referred to the anatomical land-

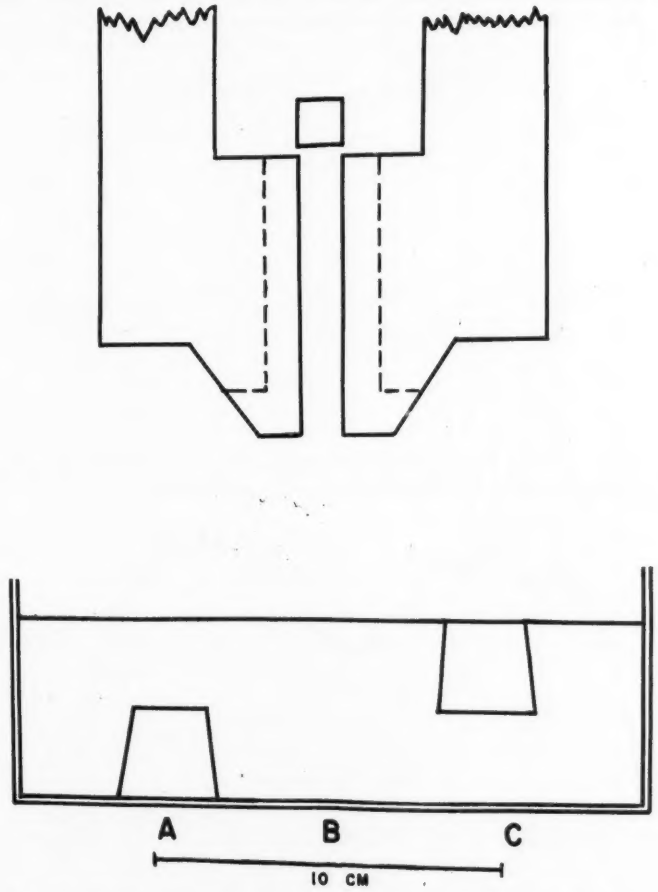

Fig. 1. **Schema of phantom and simulated defects or "tumors" displacing the radioactive solution.**

Fig. 2(a). Profile obtained over lower "tumor". The drop in counting rate (19%) is less than the decrease on the upper defect because of greater central distance.

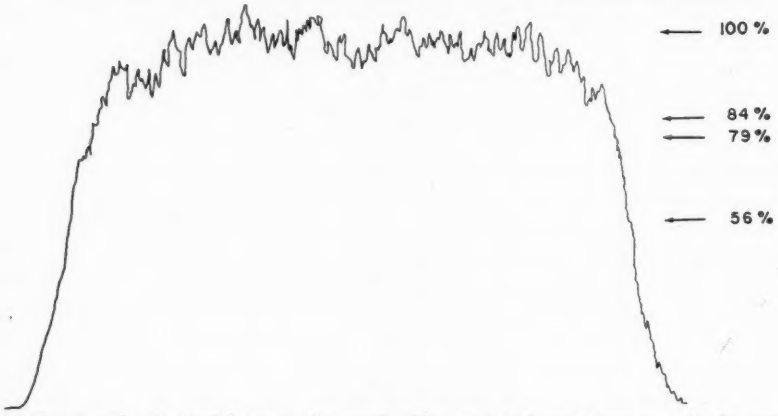

Fig. 2(b). Profile obtained between "tumors". The statistical variations seen in the profile are approximately one-third that observed in the scan.

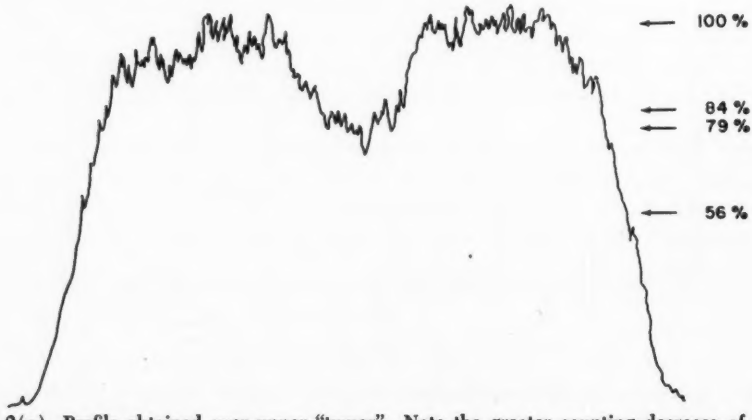

Fig. 2(c). Profile obtained over upper "tumor". Note the greater counting decrease of 28% as compared to calculated volume displacement of 23%.

Fig. 3(a). Phantom scanned at 56% cut-off level. Neither "tumor" is seen since the counting rate always exceeds this level.

(b). Phantom scanned at 79% cut-off level. Upper "tumor" clearly visualized. Lower "tumor" is partially visualized because of statistical variations in the counting rate.

(c). Phantom scanned at 84% cut-off level. Both "tumors" visualized. Small artifacts are observed because of the statistical variation in counting rate dropping below the cut-off level.

marks (xiphoid, body walls), therefore, permitting the evaluation of the size and position of the liver, as well as the changing pattern of activity over different areas referred to the corresponding lines of the dotscan.

METHOD

Following an intravenous injection of rose bengal (I^{131}) or colloidal gold (Au^{198}), a collimated scintilation counter was placed over the liver to record the accumulation of the isotope in this organ as the function of time (7). Since the majority of the cases were cancer patients screened for the presence of metastatic nodules in the liver, the dosage was not minimized and the range varied from 150 to 350 microcuries. The scintillation counter was focused over the liver for the entire period of accumulation of the radioactive material. When the plateau of concentration had been attained, the scintillation detector was motor-driven systematically over various longitudinal traverses across the abdomen (linear scanning). The colimation used consisted of a one-half-inch diameter straight bore aperture with three inches of lead shielding the crystal. The speed of the scanner was conventionally set at two inches per minute with a time constant of five seconds used in the rate meter and recorder. The parameters of both scan speed and time constants were varied, depending upon the counting rate obtained.

Following the recording of several test profiles, the counting rate cut-off circuit was adjusted to the levels consistent with the profile records. An area scan was then obtained and a series of even-spaced profiles were simultaneously recorded. Scanning parameters selected were similar to those previously reported (6).

For variations of a known displacement of radioactive material, a phantom was constructed consisting of a six-inch diameter glass container filled to a height of two inches with a solution of 350 microcuries of I^{131} in a volume of 900 milliliters of water. Rubber stoppers with dimensions of one inch in diameter and one inch in height were placed at two different depths of the container to produce a displacement of the radioactive material. The placement with relationship to the detector head is shown schematically in Fig. 1.

Fig. 4. Profile obtained at line marked on hepatoscan of Fig. 5. 300 μc of colloidal Au^{198} administered to the patient.

RESULTS

The counting rate profiles obtained by driving the detector directly over the simulated defects in the phantom are shown in Fig. 2. The decrease of 20 per cent represents the ratio of the volume of the rubber stopper to the truncated cone of radioisotope material subtended by the detector. At the collimation used

Fig. 5(a). Hepatoscan obtained with cut-off level set at 64% of the peak counting rate. 300 μc of colloidal Au^{198} administered.

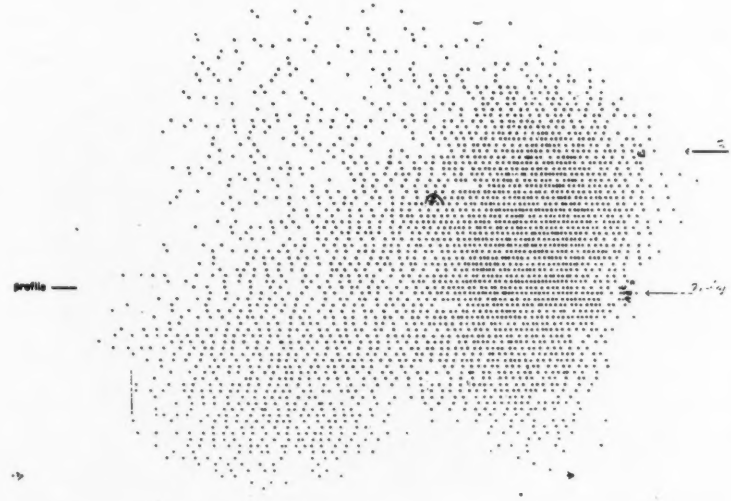

Fig. 5(b). Simultaneous hepatoscan obtained with cut-off level of 31% of the peak counting rate.

a solid angle of 2.5 degrees is expected. At a distance of 5 centimeters from the surface the volume seen by the detector is calculated to be 52 milliliters; thus, the 12 milliliter volume of the stopper would be expected to decrease the counting rate by approximately this magnitude. Some variation is seen in the counting rate over the simulated defects because of the difference in central distances to the detector.

Figure 3 shows attempts to visualize the defects in this phantom at various counting rate cut-off levels. Since a 20 per cent variation of counting rate would cause only a minor change in the number of dots recorded, the scan obtained at a cut-off level of 79 per cent of the peak value shows only a slight indication of the lower simulated defect. At a cut-off level of 84 per cent of the peak, full visualization is attained. It is customary to place the cut-off level slightly above the minimum counting rate in order to reduce the effect of random variation. As stated previously, it should be remembered that random variations will be greater in the actual scan than in the profile record. The slower speed employed in recording the profiles permitted a longer time constant, and consequently lower statistical fluctuation than with the time constant employed in the cut-off circuit of the area scan recording.

In the application of these techniques to clinical studies, Fig. 4 shows the liver profile of a patient with a gross invasion of metastatic carcinoma in the right lobe. Hepatoscans obtained at cut-off levels of 31 per cent and 64 per cent of the peak counting rate are shown in Figs. 5a and 5b. A postmortem photograph of the liver in Fig. 6 shows the invasion consistent with the radioisotope distribution.

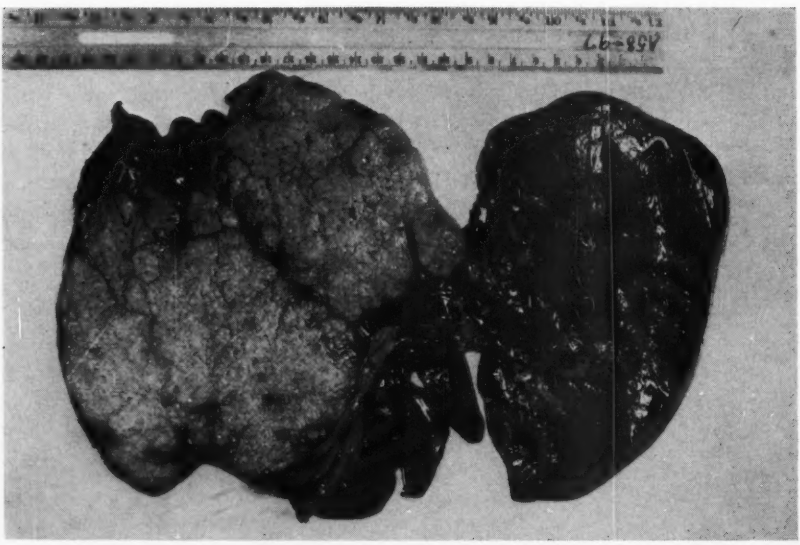

Fig. 6. **Postmortem photograph of liver showing gross invasion of metastatic carcinoma in the right lobe.**

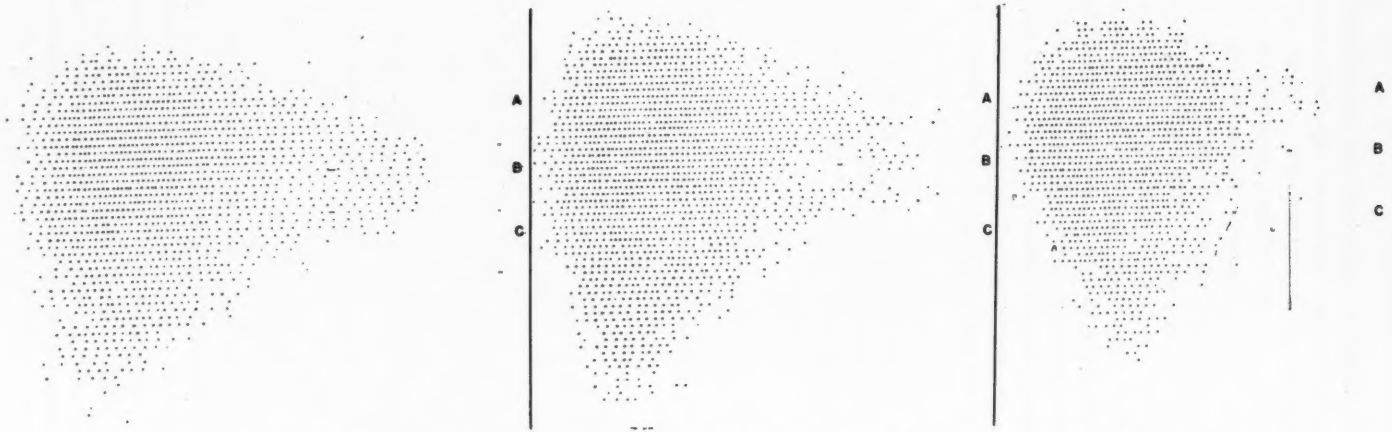

Fig. 7(a). Hepatoscan with cut-off level at 20% of the peak counting rate, following administration of 350 μc of colloidal Au^{198}.

(b). Hepatoscan with cut-off level at 41%. Note that this level set according to the profile of Fig. 8 permits the visual demonstration of the metastatic lesion in the left lobe.

(c). Hepatoscan with cut-off level at 50%. Note that this level eliminates the entire left lobe of the liver.

While the previous illustration shows essentially the same information obtained by both hepatoscans and the linear profile, this agreement is not always obvious. In Fig. 7 three hepatoscans are shown of a liver with cut-off levels set at 50 per cent, 41 per cent, and 20 per cent of the highest counting rate. The defect in the left lobe, representing a region of nonfunctioning liver tissue, is readily visualized only in the setting at the 41 per cent level. At the 50 per cent level identification is impossible because the entire left lobe is eliminated. At the 20 per cent level the decrease in counting rate is not sufficient to be perceptible to the eye. At exploratory laparotomy the patient was found to have a 2 centimeter lesion in the left lobe of the liver from carcinoma of the stomach.

The success of the hepatoscan at the 41 per cent level may be readily understood by examination of the liver profile as show in Fig. 8. The displacement of normal liver tissue occurs in the thinner part of the left lobe and corresponds to a drop in counting rate of 30 per cent with respect to the surrounding tissue. Attempts to record this small defect in the hepatoscan without accentuation have failed, as have attempts to record without a counting rate profile to indicate the setting required. A composite of juxtaposed profiles one-half inch apart recorded for this patient 90 days later is shown in Fig. 9.

DISCUSSION

Since the variation in the distribution of radioactive material in many organs may be minimal, the use of accentuation methods (8) is often necessary. The difficulty of detection without such methods has been amply illustrated both in the phantom studies and elsewhere (3, 4, 5, 6). It is obvious, however, that the appearance of the resulting scannograms will be as dependent upon the accentuation technique as it is on the original distribution. For that reason correct interpretation of such scannograms must be made with the consideration of what the actual variation in counting rate was in the original organ profile.

Fig. 8. Liver profile of preceding figure at line B. This shows a definite small dip in the profile over the left lobe indicating an area of decreased uptake. Note that a cut-off level setting of approximately 41% is necessary to demonstrate this area on the scan.

The accuracy of such recordings is based on the same parameters as any counting rate variation. Thus, the integrating time constant of the rate meters must not be excessive or the memory effect of the circuit will obscure the smaller defects. In the above examples the motor speed was greatly reduced from the usual scanning rate so as to prevent gross distortion of the spatial distribution.

In the clinical studies the profile has in some cases exhibited greater resolution than the hepatoscan itself. This is not unexpected, since longer integration times and slower speeds would result in greater accuracy. The value of the area scan is largely one of the complete visual integration of the information of radioisotope distribution rather than a summation of information from either a grid system or serial profiles. As shown above, however, the information from scanning and from the profile is often identical and thus it may result in an individual clinical opinion as to which technique is indicated for maximum useful information.

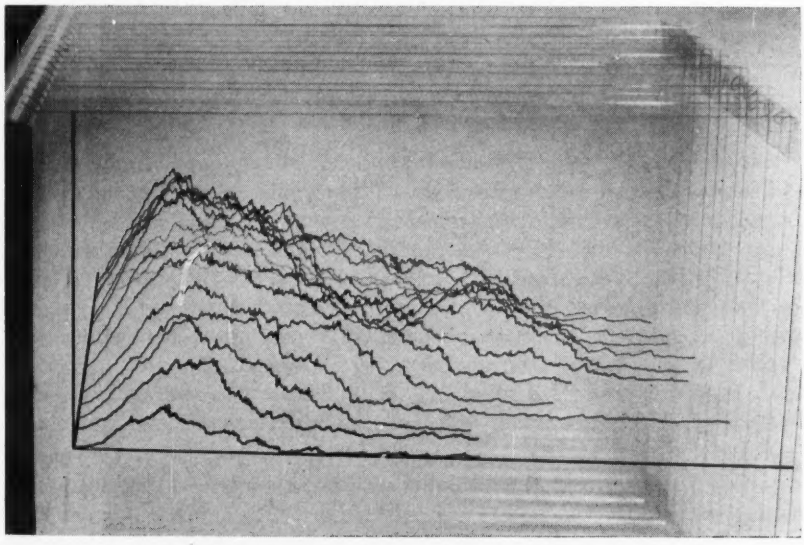

Fig. 9. Tridimensional representation of composite profiles taken one-half inch apart.

SUMMARY

In our institution it is felt that optimum results are obtained by using predotscan survey profiles for accurate setting of the cut-offs at optimum levels and utilizing both the conventional dotscan and serial profiles for interpretation. While the area scan is useful for the general organ outline, the serial profiles recorded at the time of the dotscan allow a more accurate statistical analysis of any given area for differentiation of deviation from homogeneous distribution. Since the multiple juxtaposed profiles contain all the information in a convenient visual form it is possible that this technique may supplant our present method.

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JOURNAL OF NUCLEAR MEDICINE 1:273-279, 1960

Adjuvant Use of Silver-Coated Radioactive Colloidal Gold in Treatment of Bronchogenic Carcinoma by Pneumonectomy[1]

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Nashville

INTRODUCTION

The thoracic lymph nodes constitute the most frequent site of metastases in bronchogenic carcinoma. They are followed in importance by liver, adrenal, kidney, bone, brain, heart and spleen. Rosenblatt and Lisa found lymphogenous metastases in 177 instances among 208 autopsies (1). Similar findings are recorded by Farber (2), Fried (3) and others. Thus, it might be said that the tracheobronchial and mediastinal nodes represent some of the most important sites of metastases in this condition. This is not to say that hematogenous spread is unimportant inasmuch as most surgeons agree upon an incidence of about 40 per cent in liver and adrenal metastasis. The brain is also recognized as a common site of metastases and in these three organs spread is probably by the blood stream.

For the past twelve years we have been interested in the possibility of the use of internally administered radioactive isotopes as adjuvants to the surgical treatment of bronchogenic tumors. Highly dispersed particulate gold colloids introduced transbronchially were shown to be distributed in a satisfactory manner throughout the important thoracic nodes of dogs but their movement to these sites was too slow to afford satisfactory irradiation during the short span of radioactivity of this nuclide (4). Silver colloids were shown to move readily but were uneconomical to produce and separate (5). Silver-coated radioactive colloidal gold colloids were therefore developed by us to obtain rapid translocation following endobronchial insufflation in the regional lymph nodes (6,7) and

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[1]This study was carried out under contract At-(40-1)-269 with the Division of Biology and Medicine, U. S. Atomic Energy Commission.

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were found to be well tolerated in humans (8). Beginning in 1954 such sols were administered by direct injection into the empty hemithorax following pneumonectomy (9). Administered by either route the colloid was found to be quite effectively and similarly distributed throughout the nodes of interest (10). It must be admitted that even in normal experimental animals there was some tendency toward a sporadic distribution. However, it is felt that if sufficient quantities of radioactive colloid are administered, cancericidal doses can be expected to be delivered to the thoracic lymph nodes in most instances.

We present the preliminary findings on a small group of patients, all of whom were treated by pneumonectomy in the Thayer Veterans Administration Hospital and who received adjuvant silver-coated radiogold therapy. These patients represented a contiguous series of operable resectable cases. Patients operated but excluded from the series included five in whom incomplete resection was performed and in whom for palliative reasons interstitial injection of residual tumor tissue was carried out using the silver coated radio gold colloid. These patients, however, would be placed in Category III, Table I, in our present procedure and would not be included in the treatment series involving injection of the empty chest following closure. There were no randomized controls used such as is the case in the program currently conducted by us on a national scale.

METHOD

The silver-coated radioactive gold colloid was prepared by modification of a method developed by us (6,7) and is commercially available.[1] The material was administered to the postoperative patient in most instances on the 14th day following pneumonectomy. The total amount of colloid in its predetermined dose in its original Bacterin bottle and lead shield was placed in series with a saline infusion and introduced along with approximately 100 ml of normal saline by the "wash-over technique" into the empty chest cavity. This procedure minimizes the exposure of the operator to radiation and is extremely simple. Following withdrawal of the needle from the posterior chest wall an adhesive seal is applied following which a surgical dressing is added. The latter is inspected at about twelve hour intervals for leakage which is easily discernible by the characteristic dark brown color of this sol. Any such contaminated dressings are monitored and placed in escrow for about a two week period before disposal by incineration or any other convenient means. The patient was almost invariably ambulant by the time of injection and thus, following treatment, was advised to recline and change positions frequently for the first few hours following administration in order to provide as uniform spread as possible of the material over the serosal surfaces. We have found that such patients can readily be maintained on an open ward provided 8 feet or more distance is maintained with respect to the nearest other patient's bed. Inasmuch as fairly large quantities of radiation are involved judicious attention should be paid to the amount of exposure to nursing personnel (11) for the first few days following treatment. Radioactive excreta is of no concern.

1. Obtained from Abbott Laboratories, Oak Ridge, Tennessee.

RESULTS

In this very small series it might be pointed out that there is a preponderance of incidence (about twice average) of squamous cell type tumor (2). This type is said to metastasize largely by way of the blood stream.

About half of the tumors in the patients were located on the left and half on the right side of the chest. Only one out of twelve occurred in the left lower lobe however.

We have arbitrarily (Table 1, under Resection) classified these patients as curative and non-curative. Those in whom histological examination of the nodes showed negative findings for tumor were listed under the curative resectable cases. Those in whom positive nodes were found or where extension to the pericardium or anterior chest wall occurred were listed as non-curative resections. According to such classifications four out of seven curative resectable patients were alive from two to five years following treatment. Under "category" we have used the nomenclature which is in current use by the twenty university hospital group on the adjuvant use of nitrogen mustards being conducted under the Cancer Chemotherapy National Service Center and is also being used by ourselves in a currently conducted randomized study of the silver-coated sol in therapy. In the latter system there are four categories considered: O. Operable non-resectable. I. Resectable lesion confined to one lobe of lung with no lymph node involvement. II. Lymph node involvement but surgically felt to be entirely capable of excision III. Palliative resection. Only Categories I and II are subjected to randomization and treatment in our current study. Using this classification one patient (DWa) would be affected from the surgical standpoint upon which our initial therapeutic randomization is based. This case can be described briefly as follows:

> This 60 year old Negro was admitted on March 30, 1955, with history of chest pain, shortness of breath, hemoptysis and a 10 lb weight loss. Squamous cell carcinoma of the bronchus was diagnosed by means of bronchoscopic biopsy. On April 8, 1955, under general anesthesia, right pneumonectomy was performed. At the time of operation is was felt that *possibly some tumor-bearing nodules were left in the mediastinals,* however, the patient had a lung abscess and this could not definitely be established. Fourteen days postoperatively 100 mc of silver-coated radioactive gold colloid were injected into the empty hemi-thorax. This was well tolerated and the patient was discharged several days later. He did well for three months but was readmitted on August 2, 1955, with shortness of breath, anorexia and pain in the right upper abdominal quadrant. Surgical examination showed the patient to be dyspneic with moderate tracheal shift to the right and an enlarged liver which by palpation was suspected to be carcinomatous. Despite supportive measures the patient had a rapid downhill course and died on August 10, 1955.
>
> Autopsy revealed carcinoma of the liver and recurrence of carcinoma in the bronchial stump and in the trachea. Mediastinal nodes were not involved.

TABLE 1. SUMMARY OF PATIENT DIAGNOSIS, CATEGORY, TREATMENT, AND SURVIVAL

Name	*No.*	*Type*	*Location*	*Resection*				*Category*	*Treatment Date*	*Dose mc*	*Complications*	*Date of Death*	*Survival Mo.*
				Curative		*Non-Curative*							
				Node	*Other*	*Node*	*Other*						
GGi	70677	Squamous	LUL (Lingula)			Neg.	Peri-cardium	III	10-21-57	125	None	8-28-58	10
*JWa	67524	Squamous	LUL			Neg.	Ant. Chest Wall	III	4- 5-57	114	Pulmonary Embolus with Recovery	11-23-57	7½
*HFa	67615	Squamous	LUL	Neg.				I	7-10-57	114		9- 5-57	2
*HGu	54697	Anaplastic	RML	Neg.				I	3-10-55	100	None	3- 3-56	12
DNi	74550	Squamous	RLL			Pos.		II	7-18-57	123	Broncho-pleural fistula 4-10-59	4-24-59	22

RMa	71265	Anaplastic	RML			Pos.		II	7-12-56	125	None	8-15-58	25
RMe	66601	Squamous	RUL	Neg.				I	6-16-57	125	Lobect. Tumor beyond suture line Pneumo. 5-28	L & W 6-15-60	37+
ICa	65477	Squamous	RUL	Neg.				I	6- 2-55	155	None	L & W 3- 1-60	57+
ZLa	A1041	Squamous	RLL	Neg.				I	12- 2-54	150	Thrombophlebitis	L & W 6- 4-60	67+
*DWa	55167	Squamous	RLL	Neg.				III	4- 8-55	100	None	8-10-55	4
WHa	71050	Adeno. Ca.	LLL	Neg.				I	2-19-58	125	None	L & W 2- 2-60	24+
OTh	62578	Squamous	LUL			Neg.	Ant. Chest Wall	III	8-11-54	75	None	2-27-57	30

*Bronchoscopy positive

L & W Living and Well

This patient according to our present standards would have been assigned to Category III on a surgical basis and therefore not treated with the nuclide. The possibility exists, of course, that radiological sterilization of the mediastinal nodes had been accomplished.

According to the system of treatment currently being used by us, only eight of the patients considered in this study would have been randomized for treatment with the silver-coated radio gold colloid after operation. Of these eight patients four are alive today.

DISCUSSION

In the group of patients cited above adjuvant therapy was directed primarily at the thoracic lymph nodes. It is recognized that approximately 24 per cent of cases of lung tumor show upper abdominal lymphatic metastases (1) which might not be expected to be affected by the treatment as described. However, we have recently shown that there is evidence of retrograde movement of the silver-coated colloid in the lymphatic system (10) and we trust that further studies may indicate the possible efficacy of the treatment toward such nodes.

Our studies in experimental animals have all pointed toward a rather haphazard distribution of material in the thoracic nodes following its administration either intrabronchially or into the empty hemi-thorax. This may mean that at certain times nodes and their corresponding lymphatic channels are not necessarily all in a state of equal physiological activity. Thus, if such a channel and its nodes were not receptive to transfer of colloid, perhaps neither would they be likely to move tumor tissue.

The isotope was administered to the above group of patients usually about 14 days postoperatively in contrast to the third day postoperatively as is at present being done. Also, these patients were ambulant and nearly fully recovered in contrast to those in whom the present procedure is being carried out. Ideally we should prefer to inject the material immediately following closure but upon the present system of randomization this would entail waste of 50 per cent of the material in order to have it on hand whether it was used or not.

It is generally felt that when first diagnosed approximately 50 per cent of patients with bronchogenic carcinoma are operable. Of these approximately half are looked upon as resectable which latter include the palliative resectable cases. Of the so-called "curative resectable" cases (Category I and II) a 5 year survival is generally found to occur in about 20 per cent. In the present small series the 2-5 year survival rate is about 50 per cent.

SUMMARY

Twelve cases of bronchogenic carcinoma treated by total pneumonectomy followed by adjuvant use of silver-coated radioactive colloidal gold are cited.

In this small series 4 patients are living and well at 24, 37, 57 and 67 months postoperatively. This represents approximately half of the "curative resectable" patients in the series.

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An Oscilloscope Monitor for Scintillation Spectrometers

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INTRODUCTION

Gamma-ray counting with single-channel scintillation spectrometers is an established and useful tool in nuclear medicine. However, beginning users of spectrometers are often confused by the apparent complexity of the instruments. Even operators with some experience are sometimes disturbed by misbehavior of the instruments, whether the misbehavior is major, minor, or simple misadjustment.

An auxiliary device has been developed which eliminates guesswork in adjusting a spectrometer to count a certain region of a gamma-ray spectrum. This device will also enable an operator to quickly determine whether apparent instrument failure is real or a result of misadjustment.

When the same problems arise in physics laboratories, they are dealt with by the use of a cathode ray oscilloscope. This has been a practice for many years. It usually involves an expensive oscilloscope. However, it was felt that the needs of medical scintillation spectrometry could be met by a simple oscilloscope monitor, to be used in the manner of a "tuning eye" in radio receivers.

This oscilloscope monitor is simple but effective. Since many of the functions of a conventional oscilloscope are not needed in this case, and since a spectrometer can supply many of the basic circuit requirements, it was decided to build the monitor into an existing spectrometer (1). (This has been a common practice in other fields for some time, e.g., radio transmitters, radio spectrum analyzers, tape recorders, blood cell counters and others.) Since it was built into a spectrometer, the monitor requires only three additional electron tubes and a small cathode-ray tube.

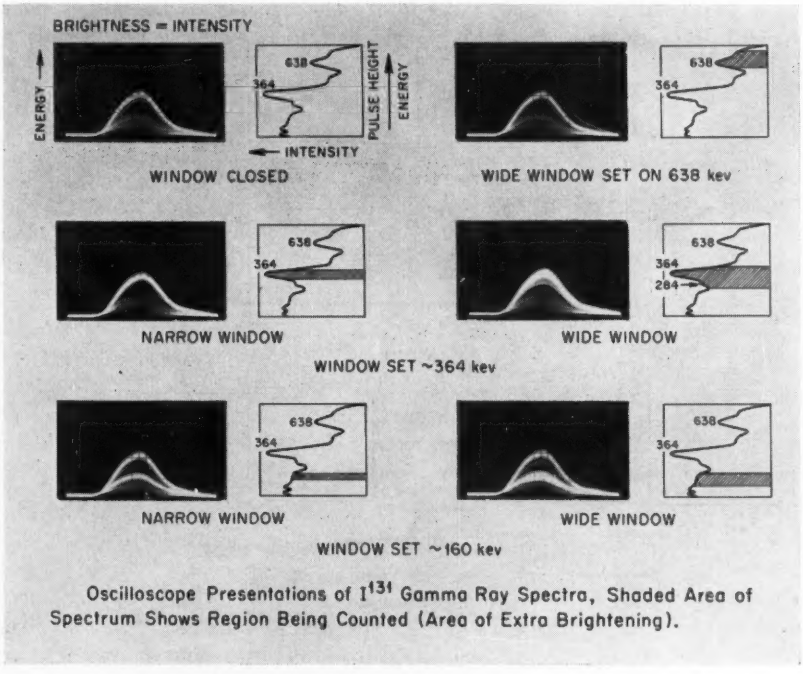
BASIC SCHEME OF OPERATION

Signals from the linear amplifier are displayed directly on the oscilloscope screen, with only a moderate brilliance or brightening. This presentation represents pulse height, or gamma-ray energy, on the vertical axis, and apparent brilliance is a measure of intensity at a given pulse height. This is shown in Fig. 1, which relates the presentation to a familiar pulse height spectrum, that of I^{131}. In addition, those pulses which are accepted for counting by the differential pulse height analyzer are given additional brightening. The combined result is a presentation which shows the operator the gamma-ray spectrum being detected and further shows exactly what portion of that spectrum is being counted.

Examples are shown in Fig. 1. Note that while the 638 Kev group is very faint, the "window can be centered on that group because of the additional brightening given to pulses "in the window". Fig. 1 also shows narrow and wide windows, respectively, set on the 364 Kev group; as well as narrow and wide windows, respectively, set in the 160 Kev region. (Note the inclusion of the 284 Kev gamma ray.)

1. Rapid and accurate centering of the "window" on a given gamma ray peak.

2. Ease of adjusment so that the entire spectrum—or desired portion thereof —is "on scale", and thus available for analyzing and counting.



Oscilloscope Presentations of I^{131} Gamma Ray Spectra, Shaded Area of Spectrum Shows Region Being Counted (Area of Extra Brightening).

Fig. 1

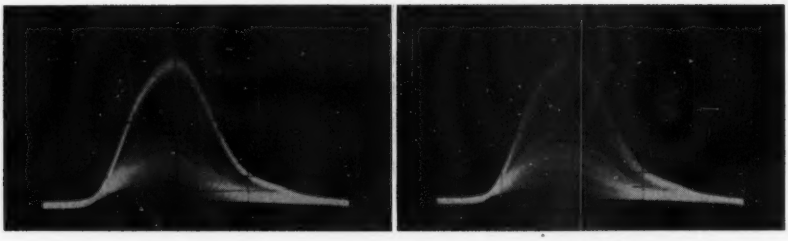


Fig. 2A Fig. 2B

Comparison of good and poor pulse height resolutions.
Fig. 2A.) 3x3 in. NaI with good resolution.
Fig. 2B.) 3x3 in. NaI with poor resolution.

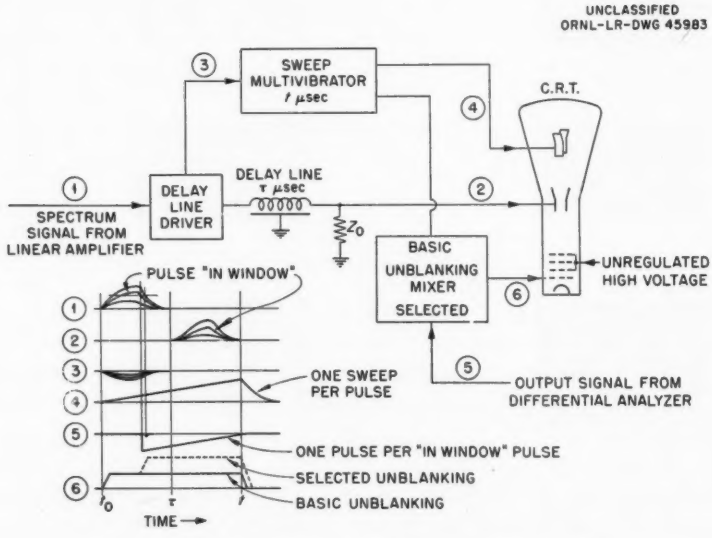
3. Definite identification of isotope—and gamma ray energies—being counted. Each isotope has a unique gamma ray spectrum as identifying as a finger print when compared to a standard source.

4. Changes in settings of the instrument, whether by drift or by accident, are shown.

5. The monitor shows evidence of proper operation of the instrument from the input to the output. Failures are noted instantly, with some indication as to location.

6. The monitor gives a direct picture of crystal-phototube resolution (Fig. 2.)

7. It is simple and inexpensive, adding only $100-$150 to the cost of the instrument. It adds only one front panel control; all oscilloscope controls are hidden.



Scintillation Spectrometer Oscilloscope Monitor: Block and Timing Diagram

Fig. 3

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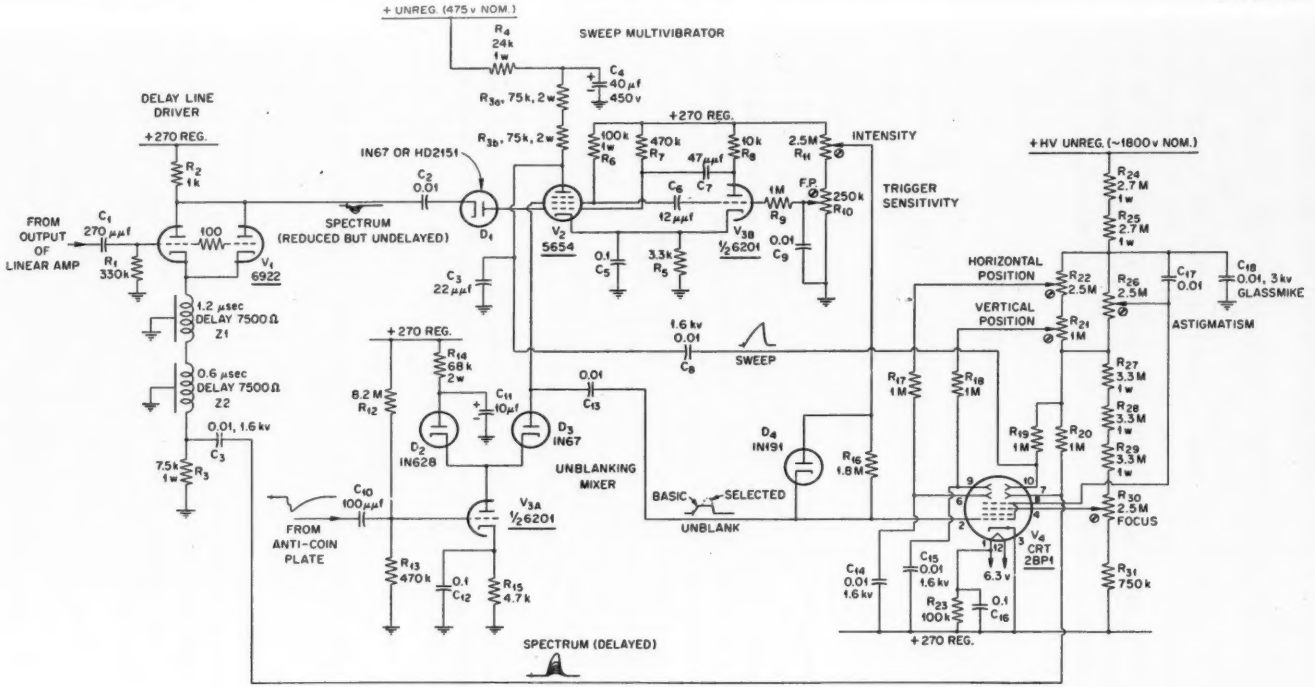

Scintillation Spectrometer Oscilloscope Monitor: Circuit Diagram.

Errata: 1. Circuit V_4 CRT 2BPI (lower right hand corner); interchange pins number 9 and 10; interchange pins number 6 and 7; interchange wiper connections to position pots so that "Horizontal Position" wiper connects with pin 10 and "Vertical Position" connects with pin 7.

2. Circuit Z_1 and Z_2 (left edge); Remove Z_2 and change Z_1 to read, 2μ sec DELAY, 7500 ohms, Z_1.
3. Circuit R_{24} and R_{25} (upper right hand corner); Remove R_{25} and change R_{24} to read, 1 M, 1_W.
4. Circuit C_{18} (upper right hand corner); Change C_{18} to read 0.1, 3Kv GLASSMIKE.

8. Reliable circuitry. The prototype has operated over two years without tube or part replacement.

The major disadvantages are offset by compensatory effects. The disadvantage of additional electronic and front-panel complexity is offset by the fact that in practical use the result has been to make operation of the instrument simpler. The drawback of more tubes and parts—which can fail—is compensated by the reliability of the monitor and by the fact that the monitor can show failures in the spectrometer. The presentation is dependent on source strength, but long persistence phosphors help with weak sources. One microcurie is quite adequate as a test source.

DETAILED EXPLANATION OF OPERATION

Attention is called to Fig. 3, which is a block diagram of the monitor. The delay line driver, VI, sends the linear amplifier signals to the vertical deflection plates of the cathode ray tube with a delay of 1.8 microseconds. This delay is necessary to establish the proper time coincidence between a pulse and evidence of its acceptance by the differential pulse height analyzer in the spectrometer. An undelayed, inverted signal is set by the delay line driver to trigger a monostable multivibrator. This multivibrator generates a sweep signal for the horizontal deflection plates of the CRT, and generates a positive pulse which "unblanks" or turns on the CRT, and gives the basic brightening to all pulses presented. The basic unblanking pulse is limited by the unblanking mixer. However, when a particular pulse is accepted by the pulse height analyzer, a signal is sent to the unblanking mixer and commands the mixer to remove the limit on the unblanking pulse. In this manner, pulses "in the window" are given extra unblanking or brightening. The accelerating voltages for the CRT is taken, unregulated, from the photomultiplier supply, as shown in the detailed circuit diagram, Fig. 4.

The monitor should be very useful to any spectrometer operator, and should be compatible with most existing spectrometers. The prototype has been found to be reliable and useful to physician, physicist, and technician alike.

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On the Method of Expressing Blood Levels in Gastrointestinal Absorption Studies[1,2,3]

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INTRODUCTION

In selecting the method of reporting blood levels in gastrointestinal absorption studies, it is desirable in the final analysis that the statistical limits of normal be as small as possible. This would result in a greater probability of detecting abnormal absorption patterns in subsequent studies of a diagnostic nature.

The two most commonly used methods of reporting blood levels in radioiodinated fat absorption studies are as percent of ingested dose per total blood volume (where the blood volume is assumed to be 7.2 per cent of the body weight) (1), and percent of ingested dose per liter of blood (2) (3). In an effort to clarify the question of which method gives a smaller range of normal, a review was made of 231 normal subjects who underwent the fat absorption study using the technique as described by Baylin, et. al. (1). This paper reports the results of the statistical analysis of the data where the blood levels were expressed as percent per total blood volume and percent per liter of blood for all of the 231 normal subjects.

METHOD

The 231 control subjects were subjected to I^{131} labeled glycerol trioleate fat absorption studies. Approximately one half of the group consisted of undergraduate students or medical students at Duke University. The balance of the group was made up of hospital patients without clinical or laboratory evidence of gastro-intestinal disease. The distribution between sexes was approximately 60-40 (with more males) since the control subjects obtained from the medical students and university students were predominantly male. The body weight ranged from 41 to 104 kilograms; the average was 64.9 kilograms.

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1. From the Department of Radiology and Department of Surgery, Duke University Medical Center, Durham, North Carolina.

2. Supported in part by U.S.P.H.S. Grant #A-836C3.

3. Presented at the Seventh Annual Meeting, Society of Nuclear Medicine, Estes Park, Colorado, June 25, 1960.

TABLE 1. BLOOD LEVELS BY WEIGHT RANGE SUBGROUPS

Number of Subjects	*Wt. Range Kg*	*Per Cent Per Liter*						*Per Cent Per Total Blood Volume*					
		4th hour		*5th hour*		*6th hour*		*4th hour*		*5th hour*		*6th hour*	
		Mean	*Std. Dev.*	*Mean*	*Std. Dev.*	*Mean*	*Std. Dev.*	*Mean*	*Std. Dev.*	*Mean*	*Std. Dev.*	*Mean*	*Std. Dev.*
231	41 to 104	2.9	.87	2.9	.83	2.8	.86	13.2	3.5	13.3	3.5	12.8	3.4
30	40 to 49	3.71	.78	3.80	.84	3.59	.80	12.2	2.3	12.4	2.5	11.8	2.6
50	50 to 59	3.27	.65	3.28	.57	3.24	.76	13.1	2.7	13.0	2.4	12.8	3.1
66	60 to 69	2.77	.74	2.77	.78	2.63	.75	12.8	3.4	12.8	3.4	12.2	3.1
60	70 to 79	2.52	.65	2.57	.61	2.49	.61	13.8	3.4	12.5	3.6	13.3	3.4
18	80 to 89	2.37	.76	2.56	.82	2.40	.80	14.2	4.4	15.3	4.7	14.5	4.8
7	90 to 104	2.09	.65	2.19	.50	2.28	.28	14.3	4.3	14.9	2.6	15.5	1.3
Maximum Deviation from Mean of 231 by any one group.		27%		31%		28.6%		8.3%		15%		21%	
Ratio of maximum observed value to minimum observed value among weight subgroupings		1.77		1.74		1.57		1.17		1.23		1.31	

The radioiodinated fat test meal was an emulsion of peanut oil and water (20:20 plus 1 part Tween 80). One milliliter of emulsion was given per kilogram of body weight. The total radioactivity in all test meals was 25 microcuries. Blood samples were drawn at the 4th, 5th, and 6th hour following ingestion of the test meal. Radioanalysis was performed on the blood samples to determine radioiodine content. This was expressed as percent per liter of blood, and percent per total blood volume for each observation.

The resultant data were analyzed for the group of 231 subjects as a whole, and by weight range subgroups. The weight ranges of the subgroups were 40 to 49 kilograms, 50 to 59 kilograms, 60 to 69 kilograms, 70 to 79 kilograms, 80 to 89 kilograms, and greater than 90 kilograms. The mean value and standard deviation were determined for the 4th, 5th, and 6th hour levels as percent per liter and percent per total blood volume.

From the results of the weight distribution study, it was apparent that there was an inverse relationship between blood concentration and body weight. Therefore, linear regressions were calculated to determine if the inverse correlation between percent per liter and body weight for each hourly sample was sig-

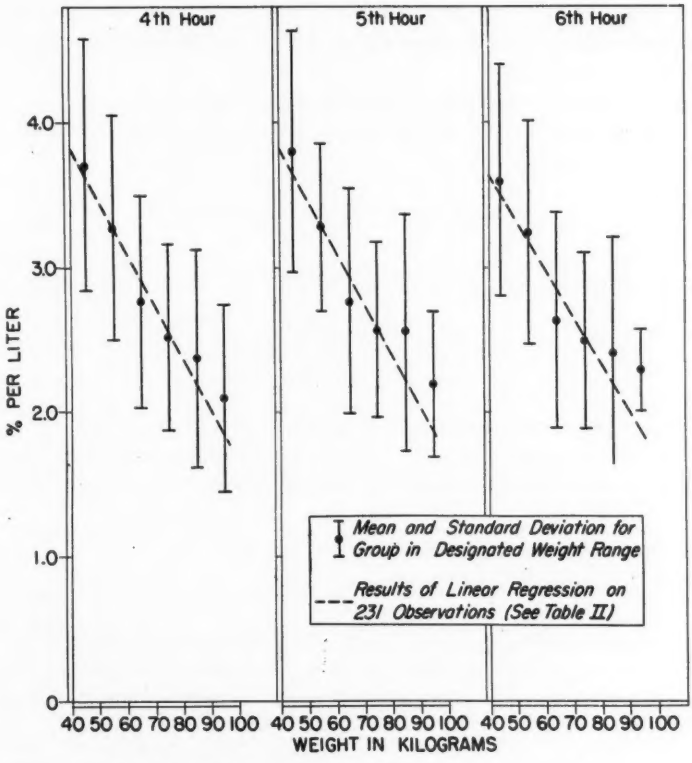

Fig. 1. Per cent per liter of blood versus body weight.

among weight subgroupings

nificantly different from zero. Similarly, linear regressions were performed on the percent per total blood volume against body weight and tested for significance with respect to zero correlation.

RESULTS

Table 1 shows the mean values and standard deviation for the group as a whole, and for the different weight range subgroupings, at the 4th, 5th, and 6th hour after ingestion of the test meal.

Figure 1 shows the results expressing the blood levels as per cent per liter as a function of body weight according to the weight range of the various groups. The mean value and standard deviation of the percent per liter of blood for each group is plotted at the mean weight distribution point for the group. The resultant linear regression curve is shown on the same graph.

Figure 2 shows the results for the mean value and standard deviation of the per cent per total blood volume for each of the weight ranges at the 4th, 5th, and 6th hour. The result of the linear regression for the entire group is shown on the same graphs.

Table 2 shows the results of the linear regression determinations for per cent per liter and per cent per total blood volume vs body weight. The equations of the resultant relationships are shown for the 4th, 5th, and 6th hour for both cases.

When a test of significance is performed on results expressed as per cent per liter versus body weight, it is seen that the inverse relationship is highly sig-

TABLE 2. LINEAR REGRESSION RESULTS

Per cent per Liter

Hour	*Equation*	*Slope* (*b*)	*Standard Deviation* (*Sb*)	*Fiducial Limit of Slope* (*P .01*)	*t*	*P*
4	y = 5.24–0.036x	−0.036	0.00362	−0.027 to −0.045	9.94	.001
5	y = 5.15–0.034x	−0.034	0.00357	−0.025 to −0.043	9.61	.001
6	y = 4.95–0.033x	−0.033	0.00383	−0.023 to −0.043	8.54	.001

Per cent per Total Blood Volume

4	y = 10.66 +0.039x	+0.039	0.018	−0.003 to +0.032	2.21	0.02
5	y = 13.1 +0.0035x	+0.0035	0.0045	−0.007 to +0.014	0.793	0.4
6	y = 12.2 +0.0059	+0.0059	0.017	−0.040 to +0.052	0.348	0.5

Where x = Body Weight in Kilograms
y = Per Cent

nificant having a probability of less than 0.001 of being zero for the 4th, 5th, and 6th hours. It is seen that the relationship between per cent per total blood volume and body weight is not significantly different from zero when a test of significance is performed. These probabilities varied from 2 per cent to greater than 50 per cent for the 4th, 5th, and 6th hour as indicated in Table 2.

DISCUSSION

One of the early observations made in our laboratory was that blood samples from small normal subjects give higher count rates than those blood samples from large patients, when an equal amount of total radioactivtiy in the fat meal was ingested. Consequently, an inverse relationship between blood concentration (per cent per liter) and body weight is expected. The results shown above; indicate that there is such an inverse relationship between blood concentration and body weight.

Maximum deviation from the mean of the entire group by any of the weight range subgroupings is much greater when the results are expressed as per cent per liter as compared to per cent per total blood volume. (Table 1) When the maximum value of any subgroup is compared to the minimum of any subgroup,

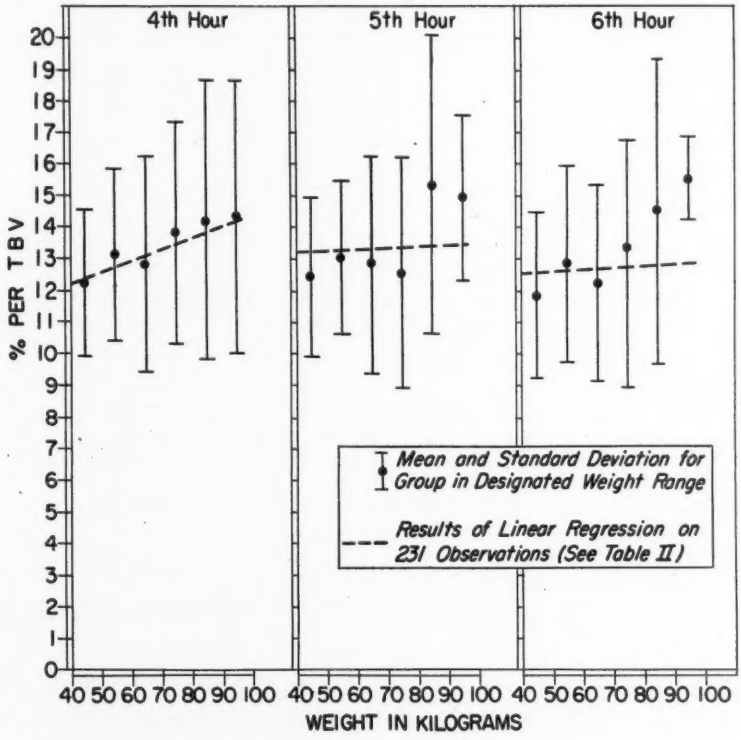

Fig. 2. Per cent per total blood volume versus body weight.

it is found that the maximum to the minimum ratio in the per cent per liter method is 1.77 for the 4th hour, 1.74 for the 5th hour, 1.57 for the 6th hour. The maximum to minimum values in the per cent per total blood volume method are 1.17, 1.23, 1.31 for the 4th, 5th, and 6th hours respectively. From these analyses, we must conclude that there is a smaller dispersion around the mean value in the per cent per total blood volume method of reporting radioactivity than in the per cent per liter method.

It is apparent from these data that there is inherent in the per cent per liter method of analysis the possibility of judging many normals as abnormal and vice versa. This is seen when you examine the lower limits of normal (P=0.05) for the 231 subjects as a whole and for the individual weight range subgroups at the 4th hour.

The lower limit of normal based upon the 231 subjects is 1.45 per cent per liter. The lower limits of normal for the weight ranges of 40 to 49 kilograms, 50 to 59 kilograms and 60 to 69 kilograms are 2.39, 2.17, and 1.53 per cent per liter. Thus any patient within these weight ranges having a blood level of 1.45 per cent per liter should be classified as abnormal. If the lower limit of normal of the entire population is used (1.45 per cent per liter, P=0.05), these patients would be erroneously classified as normal. The reverse of this situation is true for patients in the weight ranges of 80 to 89 kilograms and 90 to 104 kilograms where the lower limits of normal (P=0.05) are 1.05 and 0.86 per cent per liter respectively. Many of these patients would be classified as abnormal if the lower limits of normal for the entire population is used when actually they are within normal limits for these weight ranges.

SUMMARY

A comparison has been made of the two methods of reporting blood levels of radioactivity following a fat absorption study per cent per liter of blood, and per cent per total blood volume. An inverse relationship exists between the per cent per liter and body weight over the observed range of 40 to 100 kilograms. No definite correlation exists between the per cent per total blood volume and body weight. There is a smaller dispersion around the mean over the observed weight range of 40 to 104 kilograms when expressing the blood levels as per cent per total blood volume.

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